ADRENOCORTICAL FUNCTION IN DIABETES MELLITUS

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The undersigned hereby certify that they have read and recommend to the School of Graduate Studies for acceptance, a thesis entitled Adrenocortical Function in Diabetes Mellitus submitted by John Robert Anderson, B.E., M.D., in partial fulfilment of the requirements for the degree of Master of Science.

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ABSTRACT

The role of the adrenal cortex in diabetes mellitus has been a subject of speculation in the past decade. Reports in the literature have suggested that this disease may result in, or be associated with adrenocortical hyperfunction. Furthermore, it has been proposed that the arteriolar degenerative changes of retinopathy and nephropathy in diabetes are related etiologically to such over-activity.

The spontaneous remission of retinopathy following the onset of hypopituitarism in diabetes mellitus has lead to the use of adrenalectomy and hypophysectomy as a therapeutic measure in diabetic arteriolar disease with results which are equivocal.

Direct assessment of adrenocortical function in diabetics by the measurement of the urinary excretion of corticoids and 17-ketosteroids indicates normal or hypoadrenocorticism in the controlled diabetic. However, reports indicate an increased output of these steroids in diabetic acidosis.

Adrenal function tests measuring the eosinophil depression produced by epinephrine, A.C.T.H., or following surgery again suggest normal or hypoadrenocorticism in diabetics. The plasma 17-hydroxy-corticosteroid response to A.C.T.H. in diabetics was found to be normal by several investigators.

In this study the urinary excretion of 17-hydroxycortico-steroids and 17-ketosteroids in regulated diabetics did not differ significantly from those of control subjects. Furthermore, there was no relationship between the amounts excreted in diabetics with arteriolar disease when compared to diabetics without this complication.

Both the urinary 17-hydroxycorticosteroid and 17-ketosteroid as well as the plasma free 17-hydroxycorticosteroid response to A.C.T.H. was greater in the diabetic than in the control subject. A suggestion is offered for this phenomenon. Furthermore, there appeared to be a greater response in the diabetic with nephropathy than in the diabetic without this complication. There is insufficient evidence to be conclusive in this regard.

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A. SURVEY OF THE LITERATURE

1. The Relationship of Adreno Cortical and Pituitary Hyperfunction to Diabetes.

(a) Cushings syndrome and diabetes.

Steroid diabetes in its natural form occurs not infrequently in Cushings syndrome. The incidence is variable. In McCullagh's series of thirty-four cases of Cushings syndrome (1), twenty-one were diabetic while Plotz (2) noted diabetes in only five of thirty-three patients with this syndrome. He did, however, find decreased glucose tolerance in thirty-one of these cases.

The diabetes found in association with Cushings syndrome does, however, differ from classical diabetes mellitus in that it is usually mild, insulin resistant, reversible and not associated with acidosis or ketosis (3). In the absence of extensive glycosuria a negative nitrogen balance may exist. Nephropathy has not been reported and retinopathy is seen infrequently in Cushings syndrome (1). Unlike classical diabetes mellitus, blood pyruvate and lactate are found to be elevated before and following glucose administration in the subject with diabetes secondary to Cushings syndrome (4).

(b) Exogenous steroid diabetes.

Steroid diabetes is not an uncommon complication of prolonged glycocorticoid or A.C.T.H. therapy. It resembles the diabetes found in Cushings syndrome. Diabetics when given these substances show a marked loss of carbohydrate tolerance and many

non diabetic relatives of diabetic patients may also demonstrate abnormal glucose tolerance under these conditions (5,6).

The mechanism by which hydrocortisone and related substances produce hyperglycemia and glycosuria is not fully understood. It is known for instance that in Cushings syndrome the serum inorganic phosphorus decreases normally after the administration of glucose (3). This suggests normal peripheral utilization of carbohydrate. However, some mild diabetics also have normal phosphorus metabolism following the ingestion of glucose (3). The loss of carbohydrate tolerance in steroid diabetes is partially due to an increase in glyconeogenesis from protein, but this in itself will not account for the disorder of carbohydrate metabolism (7,8). The adrenocortical hormones may be diabetogenic due to the increased release of metabolites of the pyrimidine portions of nucleic acids which may in turn lead to the distruction of beta pancreatic cells either directly or by reducing blood glutathione (1). Decreased tubular readsorption of glucose may also be of importance (7,9).

Steroid diabetes produced by exogenous glycocorticoids or corticotropin may be a transient phenomenon. With the continuous administration of these substances, glycosuria may disappear. This suggests some compensatory mechanism (10). The same is not true in diabetes mellitus (5,6). Degranulation, hyperplasia and increased mitotic activity occur in the pancreatic beta cells of animals following the administration of A.C.T.H. or cortisone (11, 12). This most likely indicates an attempt on the part of the pancreas

to produce more insulin in order to combat the hyperglycemic effects of the adrenal steroids.

Further information regarding the inter-relationship of the beta pancreatic cells and the adrenal cortex arises from the reports that alloxan diabetic rats show adrenal cortical hypertrophy (13, 14). This does not occur if insulin is administered to control the diabetes (15).

In humans, pathologic studies of the adrenals reveal that small adenomas of the cortex occur more frequently in the diabetic than in the general population (16) and furthermore increased adrenal weight may be associated with Kimmelstiel-Wilson's syndrome (17).

(c) Hyperpituitarism and diabetes.

Several pituitary factors are known to be diabetogenic, the most important being the growth hormone and corticotropin. Furthermore, A.C.T.H. inhances the diabetogenic action of growth hormone (18). There may be yet another diabetogenic substance, the lactogenic hormone (19).

Diabetes is frequently found in association with acromegaly. In this case, growth hormone is probably the principal diabetogenic factor.

In a series of seventy-six acromegalics, McCullagh (1) found twenty-one to be diabetic. Diabetes was mild, not complicated by kidney disease, diabetic coma or gangrene. However, three of these had typical diabetic retinopathy. McCullagh feels that the absence of some of the vascular complications in these

cases can be explained on the basis of a duration of the disease too short to lead to their development.

There remains the possibility that the pituitary may in some cases of diabetes mellitus exert a diabetogenic effect through the medium of the adrenal cortex.

There are, therefore, certain similarities, but numerous differences between steroid diabetes and diabetes mellitus. The adrenal cortex, pituitary and the pancreatic islets are closely inter-related in the maintenance of normoglycemia. Perhaps some diabetics in the absence of overt clinical signs of primary hyperadrenocorticism have increased adrenal function contributing to their hyperglycemic tendancy while others may have hyperadrenocorticism secondary to the continuous metabolic stress of poor control, insulin reactions, acidosis or infections. Perhaps the vascular degenerative complications peculiar to diabetes mellitus are in some way related to adrenocortical hyperactivity as a result of continuous stress.

(d) Arteriolar disease and hyperadrenocorticism in diabetes.

The Kimmelstiel-Wilson lesion of the diabetic kidney is frequently if not always associated with retinal capillary microaneurysms, (20, 21) and it has been suggested that these are manifestations of the same vascular disease process. Furthermore, the adrenal cortex has been implicated in the pathogenesis of these lesions (17, 22).

Poor control in diabetes mellitus increases the incidence of arteriolar degenerative disease (23, 24). This may be related

to altered adrenocortical activity under these conditions. Furthermore, the aggravation of existing retinopathy or the first appearance of this condition during pregnancy (17, 25) may also result from relative adrenal hyperfunction or perhaps it may be secondary to other metabolic disturbances during pregnancy.

Lesions similar clinically to retinal microaneurysms have been produced in non diabetic persons by the prolonged administration of A.C.T.H. Furthermore, these may disappear following the withdrawal of corticotropin (17, 22). Increased urinary signs of diabetic nephropathy may follow the use of cortisone (26).

There is certain experimental evidence relating the arteriolar degenerative changes of the diabetic to the action of corticotropin or cortisone. Becker (17, 22) was able to produce what he felt to be early diabetic retinopathy in alloxan diabetic rabbits by the injection of A.C.T.H. in these animals. Flat sections of the retinae revealed microaneurysms and microscopic examination of the kidneys revealed what he considered to be intracapillary glomerulosclerosis. On the other hand with cortisone he was able to produce renal but not retinal lesions. Others have induced similar renal lesions (27, 28, 29).

11. The Relationship of Adrenocortical and Pituitary Hypofunction to Diabetes.

(a) Hypoadrenocorticism.

For many years, adrenalectomy has been known to

ameliorate experimental pancreatic diabetes. More recently D.D.D. has been shown to have essentially the same effect (30, 31).

Normal rats made diabetic with alloxan improve considerably after the administration of D.D.D. There is a lowering of blood sugar, ketonuria disappears and the animals gain weight (30). On the other hand, when D.D.D. is initially administered to normal dogs and alloxan given later, the usual diabetic picture does not develop. There may be hyperglycemia initially but the blood sugar soon returns to relatively normal levels. The adrenals of these animals show atrophy of the zona faciculata and reticularis however, the zona glomerulosa remains intact (31).

In humans it is well known that diabetes is ameliorated with the onset of Addison's Disease. Insulin requirements are much lower with adrenal insufficiency, however, the diabetes may remain very labile and there may be severe hypoglycemic reactions with relatively small doses of insulin (1, 32).

Several reports of the effect of adrenalectomy in diabetes mellitus have appeared in the literature over the past few years.

Grien (33) adrenalectomized a twenty-eight year old woman with diabetes and hypertension. She had been diabetic for twenty-two years and hypertensive for eight.

After removal of 9/10 of her adrenal tissue, she required only 1/4 her usual insulin dosage, her blood pressure fell, her cardiomegaly disappeared and urinary function improved. It is difficult to be certain whether her preoperative retinal

disease was primarily diabetic in origin, however, there was considerable improvement in her fundi. Many of these changes may be related to the effect of adrenalectomy in hypertension per se.

Wortham and Headstream (34) studied the effect of adrenalectomy in seven diabetics with advanced vascular disease. All had retinopathy.

Over a follow-up period varying from four to fourteen months, two of these were definitely improved as gaged by a reduction in oedema, subsiding retinopathy and decreased nitrogen retention with reduced proteinuria. However, three cases showed no improvement while the remaining two developed progressive renal failure. It was their opinion that the procedure was only of value in the less advanced cases.

A similar result was attained by Martin and Wilson (35) following adrenalectomy in a twenty-eight year old woman with advanced diabetic nephropathy. There was no improvement in her renal disease, she developed malignant hypertension and later died of adrenal insufficiency. More recently Graef (36) reported improvement in retinopathy in a diabetic following adrenalectomy. However, a second retinopath developed signs of nephropathy post-operatively.

Further support of the finding that adrenalectomy is of limited value in advanced diabetic arteriolar disease is added by Malins (37) who totally adrenalectomized six diabetics with retinopathy. One was improved while two with pre-operative evidence of

renal involvement were unchanged. Ease of diabetic control, insulin requirements and blood pressure were unaltered.

In summary, adrenalectomy is of some value in early diabetic arteriolar disease, but its use when this is advanced, particularly in the presence of nephropathy appears to be contra-indicated.

(b) Hypopituitarism.

The effect of hypopituitarism in diabetes mellitus is well documented. Houssay, years ago, described the amelioration of this disease in animals following hypophysectomy. Perhaps this may be due at least in part to the resultant decrease in adrenal activity.

The onset of hypopituitarism in diabetes, as with the development of hypoadrenocorticism in that disease, is accompanied by lowered insulin requirements (38, 39, 40, 41, 42). Occasionally insulin may be completely withdrawn without the appearance of glycosuria (38, 41, 42) although glucose tolerance may remain abnormal (41, 42). Diabetes sometimes associated with acromegaly may disappear following the onset of hypopituitarism (43).

Pituitary necrosis may be present to some degree in diabetes in the absence of clinical signs of hypopituitarism. Brennan (44) reported five pathologically proven instances in which this occurred. He found an incidence of some degree of pituitary necrosis of 1/50 in diabetics at autopsy compared with a ratio of 1/550 for the general population. All pituitaries presented an identical pattern of healed necrosis, the etiology of which remained obscure.

Hormonal suppression of the pituitary gland in diabetes mellitus has been studied by several investigators. Hypoadrenalcorticism following testosterone administration has been reported (45, 46).

Venning and Brown (45) determined the effect of testosterone on the urinary excretion of glycogenic corticoids and ketosteroids in two diabetics, two cases of Cushings syndrome and three normal subjects. They demonstrated a reduction in urinary ketosteroid excretion in all subjects and of glycogenic corticoids in all but one case of Cushings syndrome. They felt that this effect was secondary to the suppression of pituitary A.C.T.H. production.

It is of interest to note in this regard that testosterone therapy may be of value in the control of diabetic retinopathy (47) however, this has not been confirmed (17, 48). Estrogenic substances may also be of value in suppression of pituitary function in diabetes. Normal glucose tolerance in acromegaly has followed the prolonged use of estrogens (1). Furthermore, estrogens may be partially responsible for the prevention of retinal changes in diabetics since normal estrogen withdrawal at the menopause is frequently associated with retinal bleeding (49).

Hypophysectomy in advanced diabetes mellitus is a fairly recent procedure. Its effect on diabetes and its complications has yet to be fully assessed. The observation by Poulsen (40) of the disappearance of retinopathy following the onset of Simmonds disease has been an important stimulus to the investigation of the value of hypophysectomy in diabetes.

Luft et al (50, 51) have presented their results of hypophysectomy in a follow-up of twenty diabetics aged twenty to thirty-three years. Their period of post-operative observation varied from three to forty-three months. All their cases had retinopathy and most had an elevated blood pressure with signs of renal arteriolar disease. Death occurred in seven cases at times varying from the immediate post-operative period to nineteen months following surgery. They felt that the procedure was effective in producing a fall in blood pressure with a resultant decrease in cardiac volume. They noted a decrease in proteinuria with improvement in renal function. Some cases had subjective improvement in vision with an arrest in retinopathy. Peripheral vascular calcification, if present pre-operatively did not regress. There was, however, no development of this anomaly post-operatively. As with adrenalectomy, hypophysectomy resulted in increased insulin sensitivity with decreased requirements.

Kinsell (52) in assessing the value of hypophysectomy in four diabetics with advanced vascular disease, felt that the procedure should be reserved for those cases with evidence of progressive retinal or renal disease, but that the procedure should not be attempted in those patients with poor renal reserve. Two of his patients died, one of renal and cardiac failure five months post-operatively and the other due to a myocardial infarct, three months following hypophysectomy. Of the remaining, one showed a significant decrease in proteinuria and the other a considerable reduction in blood pressure.

III. The Measurement of Adrenocortical Function in Diabetes Mellitus.

(a) Urinary excretion of adrenal steroids.

17-Ketosteroid excretion: The adrenal androgens are not the only steroids which appear in the urinary 17-ketosteroid fraction and furthermore not all biologically androgenic steroids are excreted as 17-ketosteroids in the urine. The measurement of urinary 17-ketosteroid excretion is, therefore, only a rough gage of adrenal activity.

Several urinary ketosteroid studies have been made in diabetes mellitus and the results indicate low (53, 54, 55, 56) or normal (57) excretion in the controlled patient.

Albright (53) attributed low urinary levels to advanced age in three of his six cases. Miller and Mason (55) in an extensive study of sixty-four adult and seventeen juvenile diabetics felt that irrespective of age, urinary 17-ketosteroid excretion was lower than normal. They were unable to relate the degree of lowering to the severity of the diabetes. Development may be delayed in the juvenile diabetic and this may further contribute to decreased excretion of urinary 17-ketosteroids.

The diabetic under the metabolic stress of acidosis excretes greater than normal amounts of 17-ketosteroids in the urine. Greenman et al (57) in a study of twelve juvenile diabetics, admitted to hospital in acidosis, found that urinary 17-ketosteroid levels were two to five times normal initially, but with therapy these returned to normal. Even in the absence of acidosis poorly

controlled diabetics may excrete greater than normal levels of urinary 17-ketosteroids (58).

Corticoid Excretion: Adrenal activity in diabetes mellitus has been more accurately assessed by the measurement of the urinary excretion of glycogenic corticoids. This has been complicated by the many analytical methods which have evolved, each probably measuring a slightly different adrenal steroid fraction.

As with 17-ketosteroid studies, urinary corticosteroid levels have been found to be normal (45, 56, 59) or low (58, 60) in controlled diabetes mellitus.

Although Wolfe and Paschke's (58) in their study of urinary formaldehydogenic sterols in forty-two diabetics found lower than normal values in the majority of cases, twenty-four percent excreted relatively normal amounts and a few greater than normal quantities. On the basis of concurrent Cushings syndrome, thyrotoxicosis or diabetic acidosis only one case with increased steroid excretion was unaccountable.

It is of interest to note that Maengwyn-Davies et al (59) reported a statistically high urinary excretion of 17-hydroxycorticosteroids in diabetics with retinopathy than in those without retinal disease. However, the values found in each group fell within their normal range.

Urinary corticosteroid excretion studies have added further evidence of hyperadrenocorticism in diabetic acidosis, both in man (61, 62, 63, 64) and experimental animals (65, 66, 67).

The urinary 11-oxysteroid output was 4-23 times greater during acidosis than it was upon recovery in eleven cases described by Stowers (61). McArthur (62) found urinary corticoids to be 2-8 times greater in acidosis. Relatively lower levels have been reported in alloxan diabetic dogs (65).

One of McArthur's patients who had advanced renal disease failed to show an increased corticoid output while in acidosis. Of further interest is the direct correlation which he found between the severity of the acidosis as judged by the CO_2 combining power and the rate of corticoid excretion. Furthermore, he was able to demonstrate that urinary corticoid excretion remained normal if sufficient insulin was administered to just prevent ketonuria even though a heavy glycosuria persisted (63). This remains controversial (58). Fasting alone will prevent ketonuria and return elevated urinary corticoids to normal in the rat (67).

Brown (64) in an excellent review article on the subject of adrenal function in diabetic acidosis gives evidence to support his feeling that increased adrenal function is secondary to the acidosis and not the cause of that syndrome.

(b) Circulating adrenal corticoids.

Recently methods for the determination of circulating

17-hydroxycorticosteroids have been developed. Levels have been measured in diabetes mellitus under conditions of control (56, 68, 69, 70, 71) acidosis (56, 64, 69, 72) and during the administration of A.C.T.H. (70, 73).

In controlled diabetes, normal values are usual (56, 68, 69, 70) although elevated levels have been reported in the juvenile patient (73).

As in the case of urinary 17-ketosteroids and corticosteroids, acidosis is accompanied by elevation of circulating 17-hydroxycorticosteroids (56, 64, 68, 72).

The effect of kidney disease on urinary and plasma corticoid levels is not definitely known. In some cases of glomerulonephritis low urinary levels have been found in association with elevated circulating corticoids (56). However, circulating levels appear to be normal in diabetic nephropathy (56, 71).

In a study of free plasma corticoids in seventy-nine juvenile diabetics Klein et al (73) were able to show that even in the absence of acetonuria, the level of plasma corticoids paralleled urinary glucose excretion. In acidosis an inverse relationship existed between circulating corticoids and serum CO_2 content.

(c) Eosinophil depression studies.

The fall in circulating eosinophils following surgery, epinephrine and A.C.T.H. administration has been investigated in diabetes mellitus.

In a study of the effect of the stress of surgery in the diabetic, Field and Marble, (74) found a subnormal post-operative eosinopenia in ten of their twenty-five cases. Furthermore, the administration of A.C.T.H. to five of the ten failed to produce a normal depression in circulating eosinophils. Similar results were obtained by Grinspoon et al (75) in their study of the depression in circulating eosinophils produced by epinephrine and A.C.T.H. in fifty-nine juvenile diabetics.

A subnormal eosinopenia following A.C.T.H. administration may be more common in the diabetic with retinopathy (22).

Eosinophil depression is, however, a non-specific effect although it often bears a close relationship to adrenal cortical function. A better index is the measurement of circulating 17-hydroxycorticosteroids during the administration of A.C.T.H. There are, however, only two such studies of the diabetic in the literature.

Eik-Nes (70) administered A.C.T.H. intravenously to eight adult diabetics and thirty-nine normal subjects over a six hour period. The magnitude of rise in the circulating corticoids was similar in both groups. Klein (73) also found a normal corticoid respone to A.C.T.H. in the juvenile diabetic.

B. CLINICAL MATERIAL AND METHODS OF INVESTIGATION

1. Selection of Patients.

Patients selected for this investigation were routine admissions to hospital. Each was assessed clinically, special attention being placed on the severity, duration and ease of control of their diabetes. On physical examination, particular note was taken on the condition of their ocular fundi, cardiovascular and renal systems. Intracapillary glomerulosclerosis was diagnosed in those diabetics of fairly long standing with persistent proteinuria and more than one of retinopathy, hypertension and nephrotic oedema.

Most patients were over forty years of age. Only patients that were afebrile and under no severe stress were considered. Diabetes was under control in all but several selected cases of acidosis. The daily insulin dosage remained constant throughout. Pregnant diabetics or those with cirrhosis, peptic ulcer or unrelated kidney disease were not included.

Control subjects were selected from the general hospital population. Many of these had little evidence of clinical disease, for example, elderly patients admitted for domiciliary care. Others had mild emphysema, obesity, compensated cardiac disease, resolved pneumonia, varicose veins and so forth. None of the control subjects were considered to have clinical conditions of a very stressful nature.

11. Methods of Investigation.

This study was divided into two parts, the first

involving the measurement of the urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids in regulated diabetic and control subjects while in the second part, plasma free 17-hydroxycorticosteroid and urinary steroids were measured before and during the administration of A.C.T.H.

(a) Urinary studies.

All determinations were carried out on twenty-four hour urine specimens collected from 7:00 A.M. one morning to 7:00 A.M. the following day. Total 17-hydroxycorticosteroids were measured by a modification of the Reddy-Jenkins-Thorn method (76). This employs the basic Porter-Silber reaction between 17-21 dihydroxycorticosteroids and phenylhydrazine with the resultant production of a poorly understood color reaction.

17-ketosteroids were also determined by means of a color reaction by the method of Holtosff and Kosh (77). The conjugated urinary forms were first hydrolized and the color was produced by the Z immerrman reaction.

Urinary creatinine was estimated in all samples in order to be certain that the urines did represent a twenty-four hour collection.

(b) Urinary and plasma studies: Response to A.C.T.H.

Preliminary studies were carried out to determine the most suitable method for the administration of A.C.T.H. in order to obtain maximal adrenal response. Reports in the literature were variable.

Bayliss and Steinbeck (78) found no further rise in

plasma 17-hydroxycorticosteroids after four hours of a continuous A.C.T.H. infusion provided the patient received at least one unit per hour. Others have reported an increased response over an eight hour period with quantities of A.C.T.H. up to 20 I.U. (79). Eik-Nes et al (80) found that maximal stimulation occurred with 15 - 25 I.U. of A.C.T.H. administered intravenously over a six hour period with no significant increase when this was carried out on two successive days.

After preliminary testing with 25 I.U. of A.C.T.H. administered intravenously over a six hour and later an eight hour period on first one and then two successive days the following test was found to produce maximal plasma corticoid response. Twenty-five I.U. of A.C.T.H. in 500 cc of normal saline administered over an eight hour period on each of two successive days. The A.C.T.H. infusion was begun at 9:00 A.M. on each of these days and blood samples were withdrawn before the infusion, at 12:00 noon, at 3:00 P.M. and at 5:00 P.M. when the infusion was completed. Final sampling was carried out at 9:00 P.M. four hours following A.C.T.H. administration.

There was an identical corticoid response with either five percent glucose or normal saline as the intravenous infusion medium. However, the latter was used exclusively.

Blood samples were taken in heparinized tubes and centrifuged within one half hour of withdrawal. The plasma was separated and refrigerated overnight before analysis.

Determination of free plasma 17-hydroxycorticosteroids was carried out by a method described by Peterson (81). This again depends on the same basic color reaction used in the analysis of urinary 17-hydroxycorticosteroids.

Urinary studies as described under that heading were carried out twenty-four hours prior to and on each day of A.C.T.H. administration.

Renal function was investigated in the diabetics by means of the P.S.P. test and in selected cases a search for urinary doubly refractile lipoid bodies was made.

Plasma free 17-hydroxycorticosteroid recovery studies were carried out concurrently in more than half the samples analyzed. Recovery of hydrocortisone added to plasma to make up a 50 mgm.% solution, varied from 81.0% to 114.2% with a mean recovery of 94.6%.

Plasma glucose levels as high as 1000 mgm.% did not influence the plasma 17-hydroxycorticosteroid levels measured by this method.

C. RESULTS

1. Urinary Studies

These are presented in the form of tables. Table 1 (1) lists the results of 17-hydroxysteroid and 17-ketosteroid excretion in sixty-five control subjects while table I (2) gives the excretion values found in ninety-six diabetic patients. Table I (3) compares the excretion levels of diabetics with arteriolar disease to those of diabetics without this complication. Other comparisons are made with respect to insulin requirements and the duration of diabetes. These are found in tables I (4) and I (5) in the appendix.

11. Urinary and Plasma Studies: Response to A.C.T.H.

In tables II (1) to II (18) are tabulated the plasma 17-hydroxycorticosteroid and the urinary 17-hydroxycorticosteroid and 17-ketosteroid response at various time intervals prior to and during the administration of A.C.T.H. in fifteen control subjects and twenty diabetics. These include comparisons of control subjects to regulated diabetics and diabetics in acidosis. Furthermore, a comparison is made between diabetics with arteriolar disease and those without this complication.

Tables II (19) to II (30) list comparisons with respect to insulin requirements and the duration of diabetes. These are included in the appendix.

I - URINARY STUDIES

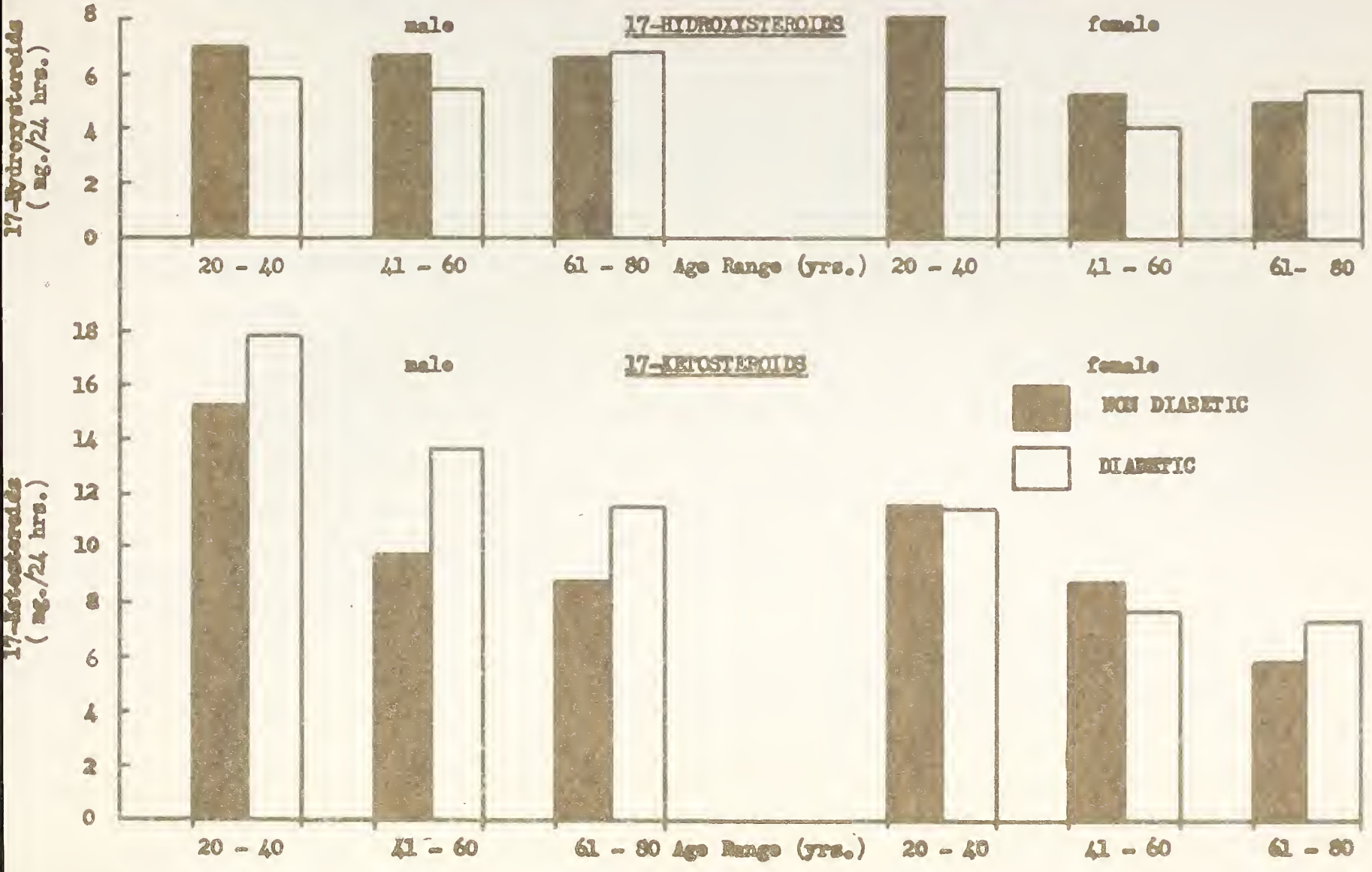
Steroids	17-Hydroxysteroids						17-Ketosteroids					
Sex	Male			Female			Male			Female		
Age range (years)	20 40	41 60	61 80	20 40	41 60	61 80	20 40	41 60	61 80	20 40	41 60	61 80
Number of cases	11	5	13	17	12	6	11	5	14	17	12	6
Steroid range (mg./24 hours)	3.09 10.1	2.51 11.0	2.88 11.1	4.34 14.5	.91 14.5	3.34 7.03	7.39 21.8	4.80 14.5	3.43 17.7	5.06 20.5	4.58 14.2	2.63 10.1
Steroid mean (mg./24 hours)	7.18	6.73	6.41	8.05	5.13	5.05	15.2	9.7	8.69	11.6	8.69	5.64
S. D.	2.31	3.47	2.20	2.69	3.58	1.60	4.7	4.34	3.75	4.1	3.08	2.82

Table I(1) 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids in control subjects.

Steroids	17-Hydroxysteroids						17-Ketosteroids					
Sex	Male			Female			Male			Female		
Age range (years)	20 40	41 60	61 80	20 40	41 60	61 80	20 40	41 60	61 80	20 40	41 60	61 80
Number of cases	18	11	25	6	6	22	19	15	24	6	6	25
Steroid range (mg./24 hours)	2.28 19.6	1.31 10.3	1.50 14.3	1.92 9.01	1.30 6.64	0.73 12.4	5.57 33.4	7.44 23.4	5.75 22.3	5.23 22.6	2.40 12.8	3.12 14.4
Steroid mean (mg./24 hours)	5.89	5.35	6.92	5.55	4.08	5.35	17.9	13.6	11.4	11.5	7.82	7.23
S. D.	5.29	2.99	3.85	2.35	2.18	3.00	6.2	4.4	4.0	6.3	3.72	2.99

TABLE I(2) 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids in diabetics.

FIGURE I THE 24-HOUR URINARY EXCRETION OF 17-HYDROXYSTEROIDS AND 17-KETOSTEROIDS IN DIABETIC AND NON DIABETIC PERSONS.

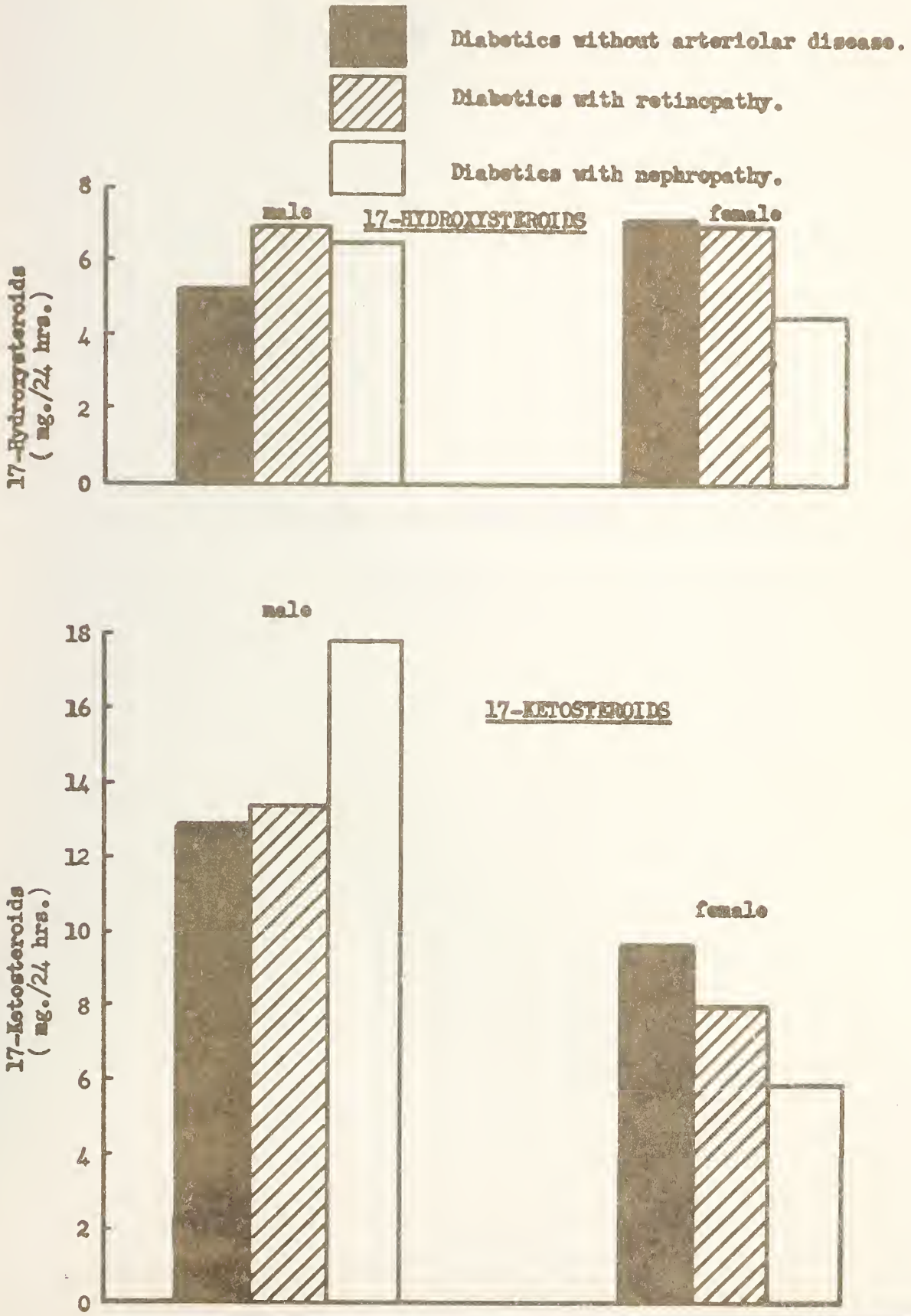


Steroids	17-Hydroxysteroids						17-Ketosteroids					
Sex	Male			Female			Male			Female		
Complications*	W	R	N	W	R	N	W	R	N	W	R	N
Number of cases	40	13	11	20	8	9	42	12	12	23	8	9
Average age (years)	50	56	46	56	62	59	50	56	46	56	62	59
Steroid range (mg./24 hours)	0.53 13.2	2.03 11.2	2.55 19.6	0.73 22.3	1.66 9.01	1.92 8.40	4.30 24.6	7.44 22.3	9.03 33.4	2.40 22.6	4.12 13.0	3.12 12.9
Steroid mean (mg./24 hours)	5.14	6.95	6.50	5.46	5.18	4.40	12.9	13.2	17.8	9.69	7.98	5.91
S. D.	3.27	2.92	5.19	4.68	2.68	2.04	5.0	4.3	6.3	4.56	3.21	2.93

* W- Without arteriolar complications.
R- With retinopathy but not nephropathy.
N- With nephropathy.

TABLE I(3) 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids. A comparison of those diabetics with arteriolar disease to those without this complication.

FIGURE II THE 24-HOUR URINARY EXCRETION OF 17-HYDROXYSTEROIDS AND 17-KETOSTEROIDS IN THE DIABETIC WITH AND WITHOUT ARTERIOLAR DISEASE.



II - URINARY AND PLASMA STUDIES:

RESPONSE TO

A.C.T.H.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	11	3	14	12	2	14	12	3	15	12	3	15	10	1	11
Range 17-OHCS gm./100 cc	2.5 22.4	10.7 13.7	2.5 28.7	12.0 46.0	32.6 36.2	12.0 46.0	153 63.5	38.6 40.0	15.3 47.1	19.5 65.8	34.6 42.6	19.5 65.8	19.3 42.8	—	19.3 42.8
Mean 17-OHCs ¥gm./100 cc	9.9	12.5	10.4	26.2	34.4	27.4	36.6	39.4	37.2	37.1	38.8	37.4	29.5	42.1	30.6
S. D.	8.3	1.6	7.5	10.4	-	10.0	11.8	0.7	10.5	10.8	4.0	9.7	8.3	-	8.7

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(1) Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to control subjects.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	8	6	14	10	6	16	11	6	17	11	6	17	8	6	14
Range 17-OHCS gm./100 cc	11.3 22.3	5.4 31.4	5.4 31.4	11.8 81.5	27.1 46.0	11.8 81.5	18.8 76.6	41.7 64.9	18.8 76.6	28.7 64.8	40.8 66.6	28.7 66.6	18.8 57.8	34.9 73.3	18.8 73.3
Mean 17-OHCs ¥gm./100 cc	16.8	15.8	16.4	36.8	37.2	36.9	45.0	48.6	46.3	41.4	54.2	45.9	40.4	57.4	47.7
S. D.	3.9	10.4	7.1	18.4	7.7	14.9	17.3	9.3	14.7	10.2	9.5	11.6	13.2	13.1	15.4

#Hours after the beginning of ACTH administration.
*M - Male
F - Female
T - Total (male and female)

TABLE II(2) Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to regulated diabetics.

Time of Sampling #	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	2	1	3	2	1	3	2	1	3-	2	1	3	1	1	2
Range 17-OHCS gm./100 cc	5.5 26.0	-	5.5 26.0	30.5 51.4	-	30.5 51.4	31.8 56.4	-	31.8 57.6	37.9 75.0	-	37.9 75.0	-	-	56.6 74.5
Mean 17-OHCs ¥gm./100 cc	15.8	14.9	15.5	41.0	48.1	43.3	44.1	57.6	48.6	56.5	60.7	57.9	74.5	56.6	65.6
S. D.	-	-	10.3	-	-	11.2	-	-	14.6	-	-	18.7	-	-	-

//

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(3) Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics in mild acidosis.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	12	3	15	12	3	15	12	3	15	11	3	14	8	3	11
Range 17-OHCS gm./100 cc	3.0 37.5	10.3 17.6	3.0 37.5	27.4 71.8	38.6 47.6	27.4 71.8	38.6 63.3	55.5 60.9	38.6 63.3	39.6 66.6	54.8 60.8	39.6 66.6	32.1 69.9	50.1 68.0	32.1 69.9
Mean 17-OHCs gm./100 cc	14.5	11.9	14.0	46.4	42.9	45.7	51.4	57.9	52.8	54.3	57.3	54.9	50.7	57.4	52.6
S. D.	9.2	5.0	7.9	12.7	4.5	11.5	6.7	2.7	5.4	7.4	3.3	6.9	12.1	9.4	11.4

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(4) Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to control subjects.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	10	6	16	11	6	17	10	.6	16	11	6	17	10	6	16
Range 17-OHCS gm./100 cc	8.8 570	8.9 97.5	8.8 97.5	28.8 81.0	46.5 79.4	28.8 81.0	41.0 93.0	49.9 105.0	41.0 105.0	49.0 81.6	46.9 133.0	46.9 133.0	28.9 85.0	22.8 97.5	22.8 97.5
Mean 17-OHCs ¥gm./100 cc	25.0	48.7	33.9	54.5	66.3	58.7	64.2	79.6	70.0	63.7	79.1	69.1	54.0	69.8	59.9
S. D.	16.8	32.5	25.8	14.8	12.0	14.7	15.5	18.5	17.9	12.1	29.6	21.6	20.6	29.2	24.6

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(5) Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to regulated diabetics.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	2	1	3	2	1	3	2	1	3	2	1	3	2	1	3
Range 17-OHCS gm./100 cc	9.0 33.7	-	9.0 33.7	54.1 77.4	-	54.1 77.4	59.4 105.0	-	59.4 105.0	53.5 117.0	-	53.5 117.0	39.0 109.0	-	39.0 109.0
Mean 17-OHCs ɣgm./100 cc	21.4	24.1	22.3	65.8	64.5	65.3	82.2	70.0	78.1	85.3	82.9	84.5	74.0	85.1	77.7
S. D.	-	-	12.4	-	-	11.7	-	-	22.8	-	-	31.8	-	-	35.7

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(6) Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics in mild acidosis.

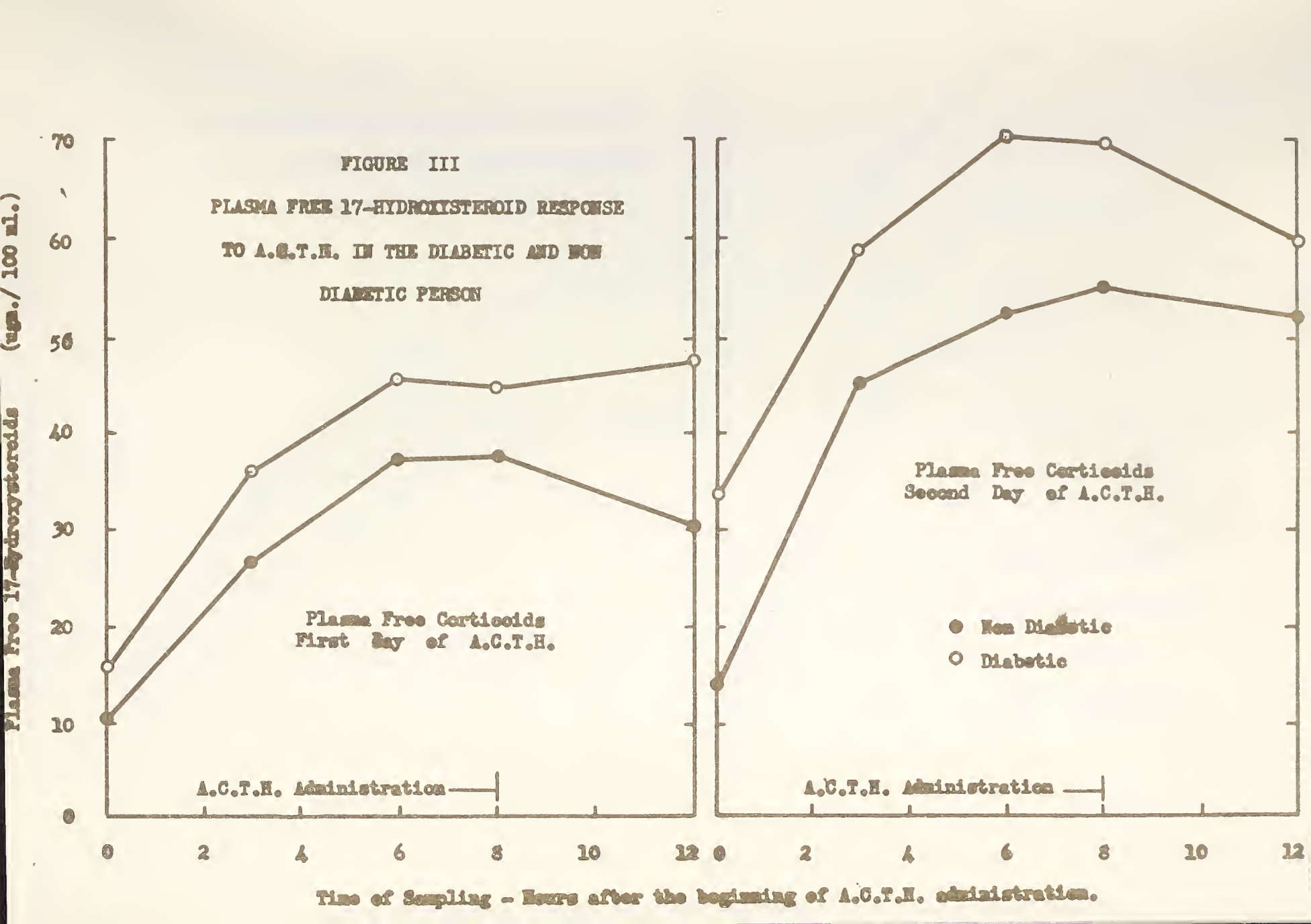


FIGURE III
PLASMA FREE 17-HYDROXYSTEROID RESPONSE
TO A.C.T.H. IN THE DIABETIC AND NON
DIABETIC PERSON
Plasma Free 17-Hydroxysteroids (mgm./ 100 ml.)
70
60
50
40
30
20
10
0
Plasma Free Corticoids
First Day of A.C.T.H.
A.C.T.H. Administration
0
2
4
6
8
10
12
Plasma Free Corticoids
Second Day of A.C.T.H.
Non Diabetic
Diabetic
A.C.T.H. Administration
Time of Sampling - Hours after the beginning of A.C.T.H. administration.

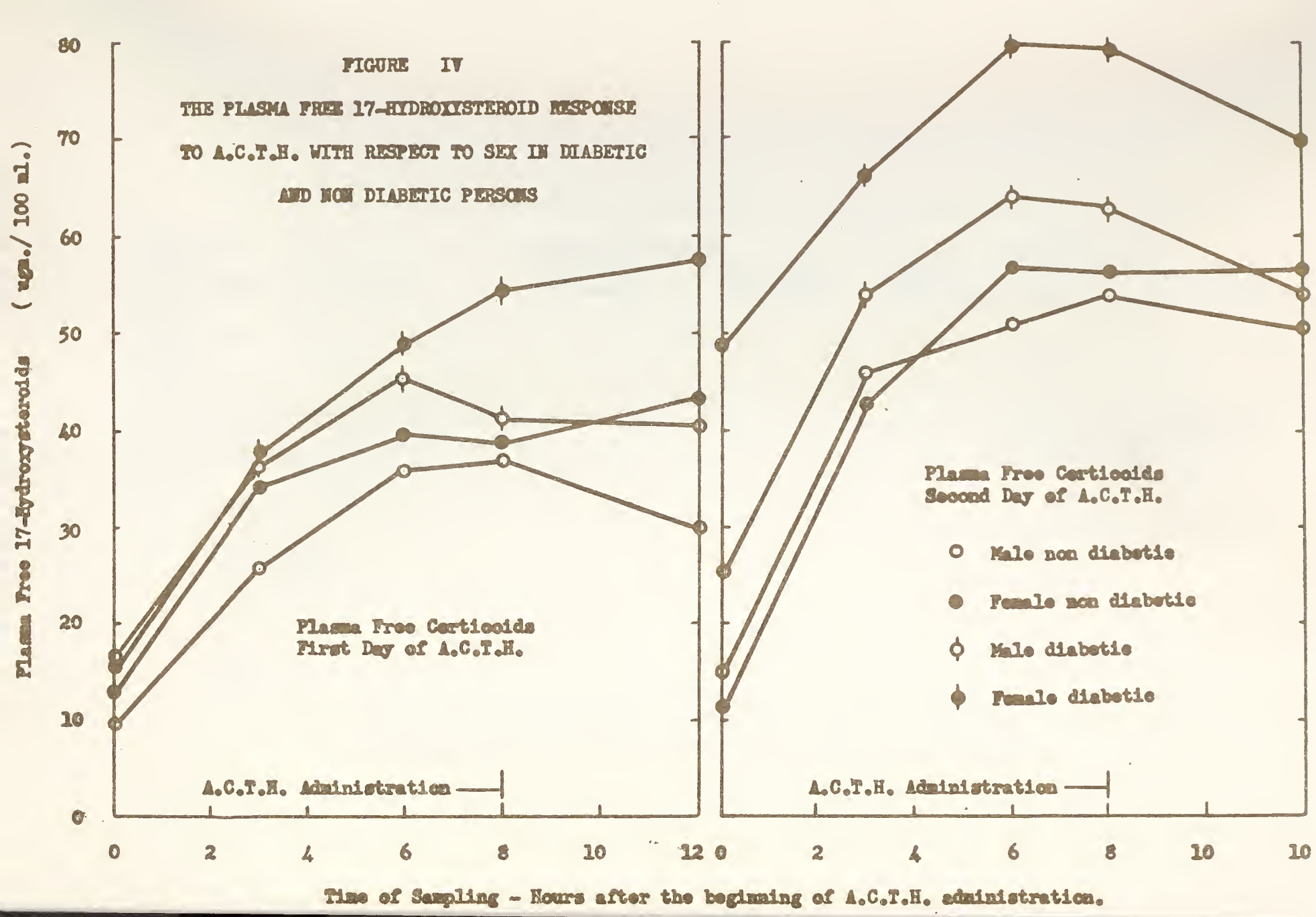


FIGURE IV
THE PLASMA FREE 17-HYDROXYSTEROID RESPONSE
TO A.C.T.H. WITH RESPECT TO SEX IN DIABETIC
AND NON DIABETIC PERSONS
Plasma Free 17-Hydroxysteroids (ugm./ 100 ml.)
80
70
60
50
40
30
20
10
0
Plasma Free Corticoids
First Day of A.C.T.H.
A.C.T.H. Administration
0
2
4
6
8
10
12
Plasma Free Corticoids
Second Day of A.C.T.H.
Male non diabetic
Female non diabetic
Male diabetic
Female diabetic
A.C.T.H. Administration
0
2
4
6
8
10
10
Time of Sampling - Hours after the beginning of A.C.T.H. administration.

Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	11	2	13	12	2	14	12	3	15	11	2	12	2	12	3
Steroid Range (mg./24 hours)	2.9 11.9	3.3 9.4	2.9 11.1	11.9 35.4	17.8 18.9	11.9 35.4	23.5 57.2	28.8 39.7	23.5 57.2	3.4 17.7	7.3 7.4	8.9 30.1	10.0 11.7	9.9 38.2	17.0 22.1
Steroid Mean (mg./24 hours)	6.9	6.4	6.8	22.2	18.4	21.6	37.9	32.8	36.9	9.5	7.3	16.8	10.9	21.5	20.1
S. D.	2.2	-	2.4	7.3	-	6.9	11.7	5.8	10.8	3.8	-	6.4	-	8.7	2.6

* M - Male
F - Female
T - Total (Male and Female)

TABLE II(7) 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. of ACTH over an eight hour period on each of two days to the control subject.

Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	11	5	16	9	5	14	11	5	16	11	5	9	5	11	5
Steroid Range (mg./24 hours)	2.30 14.3	2.35 7.38	2.30 14.3	13.9 42.8	6.88 43.9	6.88 43.9	22.8 82.8	16.4 69.6	16.4 82.8	8.01 18.2	5.08 8.47	9.00 26.2	6.70 17.6	11.3 40.8	9.80 36.5
Steroid Mean (mg./24 hours)	7.51	4.57	6.60	29.0	22.9	26.9	43.7	39.7	42.4	12.7	6.90	20.2	12.2	29.4	21.3
S. D.	3.92	2.46	4.24	8.5	17.3	12.1	21.4	20.8	20.6	3.7	1.20	5.9	7.1	9.0	10.4

* M - Male
F - Female
T - Total (Male and Female)

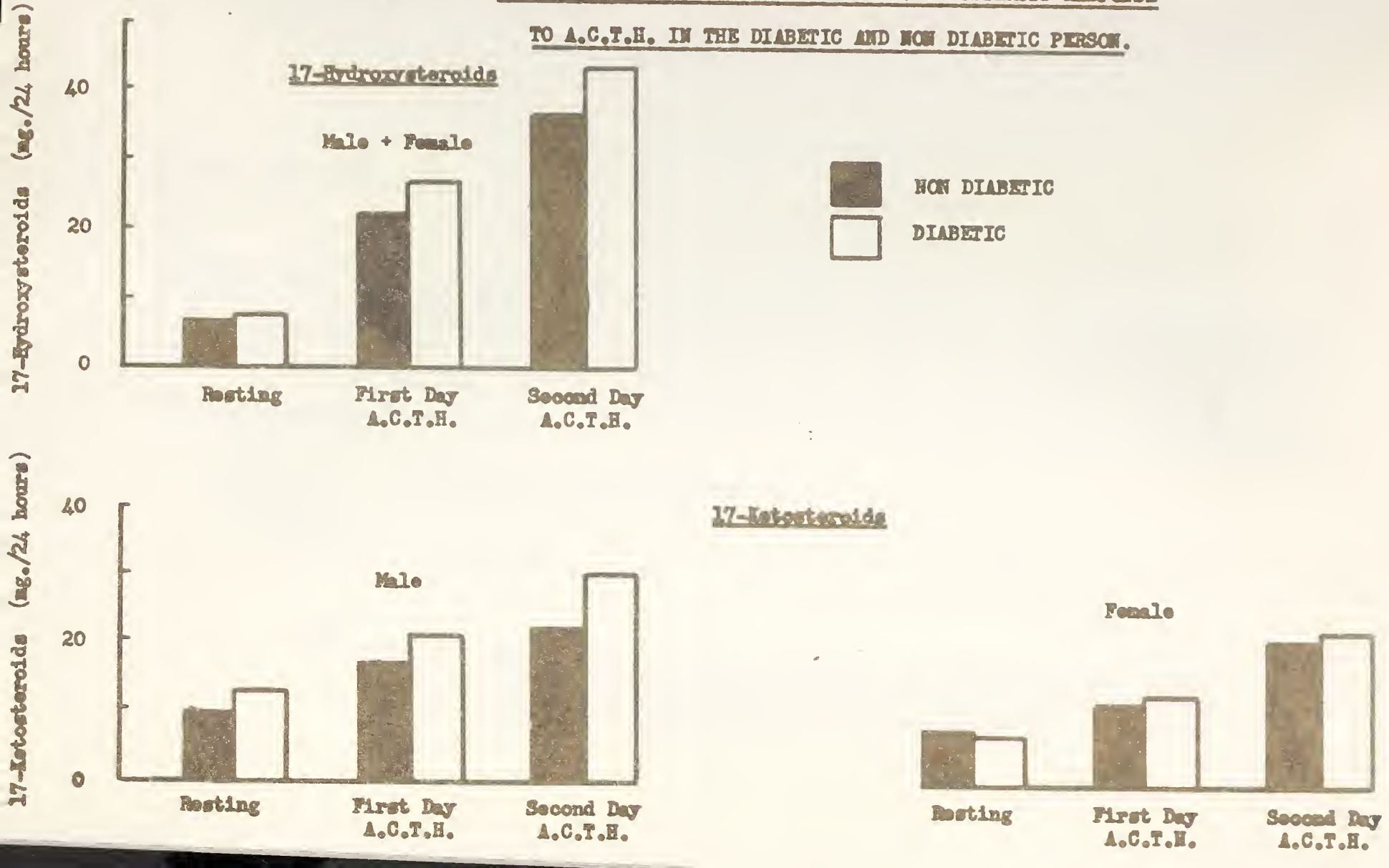
TABLE II(8) 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. of ACTH over an eight hour period on each of two days to the regulated diabetic.

Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	2	1	3	2	-	-	2	1	3	2	1	2	-	2	1
Steroid Range (mg./24 hours)	3.0 7.9	-	3.0 7.9	9.9 16.6	-	-	11.0 29.0	-	11.0 67.0	5.5 7.9	-	8.6 12.5	-	9.2 14.9	-
Steroid Mean (mg./24 hours)	5.4	4.5	5.1	13.2	-	-	20.0	67.0	35.7	6.7	4.8	10.6	-	12.0	50.3
S. D.	-	-	2.5	-	-	-	-	-	28.6	-	-	-	-	-	-

* M - Male
F - Female
T - Total (Male and Female)

TABLE II(9) 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. ACTH over an eight hour period on each of two days to diabetics in mild acidosis.

FIGURE V THE URINARY 17-HYDROXYSTEROID AND 17-KETOSTEROID RESPONSE TO A.C.T.H. IN THE DIABETIC AND NON DIABETIC PERSON.



Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	4	3	7	5	3	8	5	3	8	5	3	8	3	3	6
Range 17-OHCS gm./100 cc	11.3 22.3	8.6 12.0	8.6 22.3	11.8 48.4	27.1 40.8	11.8 48.4	18.8 63.6	41.7 44.1	18.8 63.6	30.1 64.8	40.8 66.6	30.1 66.6	18.8 57.8	34.9 65.2	18.8 65.2
Mean 17-OHCs ɣgm./100 cc	15.3	10.7	13.4	32.9	35.5	33.9	46.9	43.9	45.4	42.9	55.1	47.5	39.4	51.0	45.2
S. D.	4.9	1.9	4.4	13.9	7.3	11.3	19.8	1.8	15.2	13.8	13.1	14.0	19.6	15.3	16.9

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(10) Relationship of diabetic arteriolar disease to adrenal function. Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics without arteriolar disease.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	4	3	7	5	3	8	6	3	9	6	3	9	5	3	8
Range 17-OHCS gm./100 cc	14.4 20.0	5.4 31.4	5.4 31.4	26.8 81.5	28.6 46.0	26.8 81.5	32.2 76.6	43.7 64.9	32.2 76.6	28.7 51.1	45.7 60.2	28.7 60.2	24.6 53.0	57.0 73.3	24.6 73.3
Mean 17-OHCs ¥gm./100 cc	18.2	20.9	19.4	40.6	39.0	40.0	43.5	54.4	47.2	40.1	53.3	45.0	40.9	63.8	49.5
S. D.	2.6	13.7	8.2	23.1	9.2	18.1	16.7	10.6	15.2	7.4	7.3	9.6	10.6	8.4	15.1

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(11) Relationship of diabetic arteriolar disease to adrenal function. Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics with evidence of retinopathy and / or nephropathy.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	1	2	3	1	2	3	2	2	4	2	2	4	2	2	4
Range 17-OHCS gm./100 cc	-	25.8 31.4	18.6 31.4	-	28.6 42.4	28.6 v85.1	33.0 76.6	43.7 54.6	33.0 76.6	44.1 53.9	45.7 53.9	44.1 53.9	47.2 53.0	57.0 61.6	47.2 61.6
Mean 17-OHCs ɣgm./100 cc	18.6	28.6	25.3	85.1	35.5	52.0	54.8	49:2	52.0	47.6	49.8	48.7	50.1	59.3	54.7
S. D.	-	-	6.4	-	-	27.5	-	-	18.7	-	-	4.6	-	-	6.1

#Hours after the beginning of ACTH administration.
*M - Male
F - Female
T - Total (male and female)

TABLE II(12) Relationship of diabetic arteriolar disease to adrenal function. Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics with nephropathy.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	5	3	8	5	3	8	5	3	8	5	3	8	4	3	7
Range 17-OHCS gm./100 cc	8.8 24.1	8.9 41.7	8.8 41.7	28.8 62.9	46.5 73.4	28.8 73.4	41.0 75.5	49.9 87.8	41.0 87.8	49.0 81.6	46.9 133.0	46.9 133.0	28.9 85.0	22.8 97.5	22.8 97.5
Mean 17-OHCs ɣgm./100 cc	15.1	29.5	20.5	47.7	62.6	53.3	64.0	74.8	68.1	61.1	89.3	71.7	54.1	66.4	59.1
S. D.	6.4	18.0	13.0	15.5	14.3	16.1	13.8	21.8	16.5	12.7	43.0	28.9	26.9	38.8	30.4

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(13) Relationship of diabetic arteriolar disease to adrenal function. Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics without arteriolar disease.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	5	3	8	6	3	9	5	3	8	6	3	9	6	3	9
Range 17-OHCS gm./100 cc	10.6 57.0	29.2 97.5	10.6 97.5	48.8 81.0	58.0 79.4	48.8 81.0	42.6 93.0	72.5 105.0	42.6 105.0	52.7 81.5	63.0 72.5	52.7 81.5	31.8 76.0	45.1 88.1	31.8 88.1
Mean 17-OHCs ɣgm./100 cc	35.0	67.9	47.3	60.2	70.0	63.5	64.3	84.5	71.9	65.9	68.8	66.8	53.9	73.2	60.4
S. D.	18.7	35.1	29.0	12.6	10.9	12.4	18.8	17.9	20.0	12.3	5.1	10.1	18.1	24.4	21.7

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(14) Relationship of diabetic arteriolar disease to adrenal function. Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics with evidence of retinopathy and / or nephropathy.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	2	2	4	2	2	4	1	2	3	2	2	4	2	2	4
Range 17-OHCS gm./100 cc	43.4 57.0	77.0 97.5	43.4 97.5	56.2 69.5	72.5 79.4	56.2 79.4	-	75.9 105.0	62.4 105.0	57.9 80.6	71.0 72.5	57.9 80.6	45.8 76.0	86.4 88.1	45.8 88.1
Mean 17-OHCs gm./100 cc	50.2	87.3	68.7	62.9	76.0	69.4	62.4	90.3	81.1	69.3	71.8	70.5	60.9	87.3	74.1
S. D.	-	-	23.6	-	-	12.2	-	-	21.8	-	-	9.4	-	-	19.6

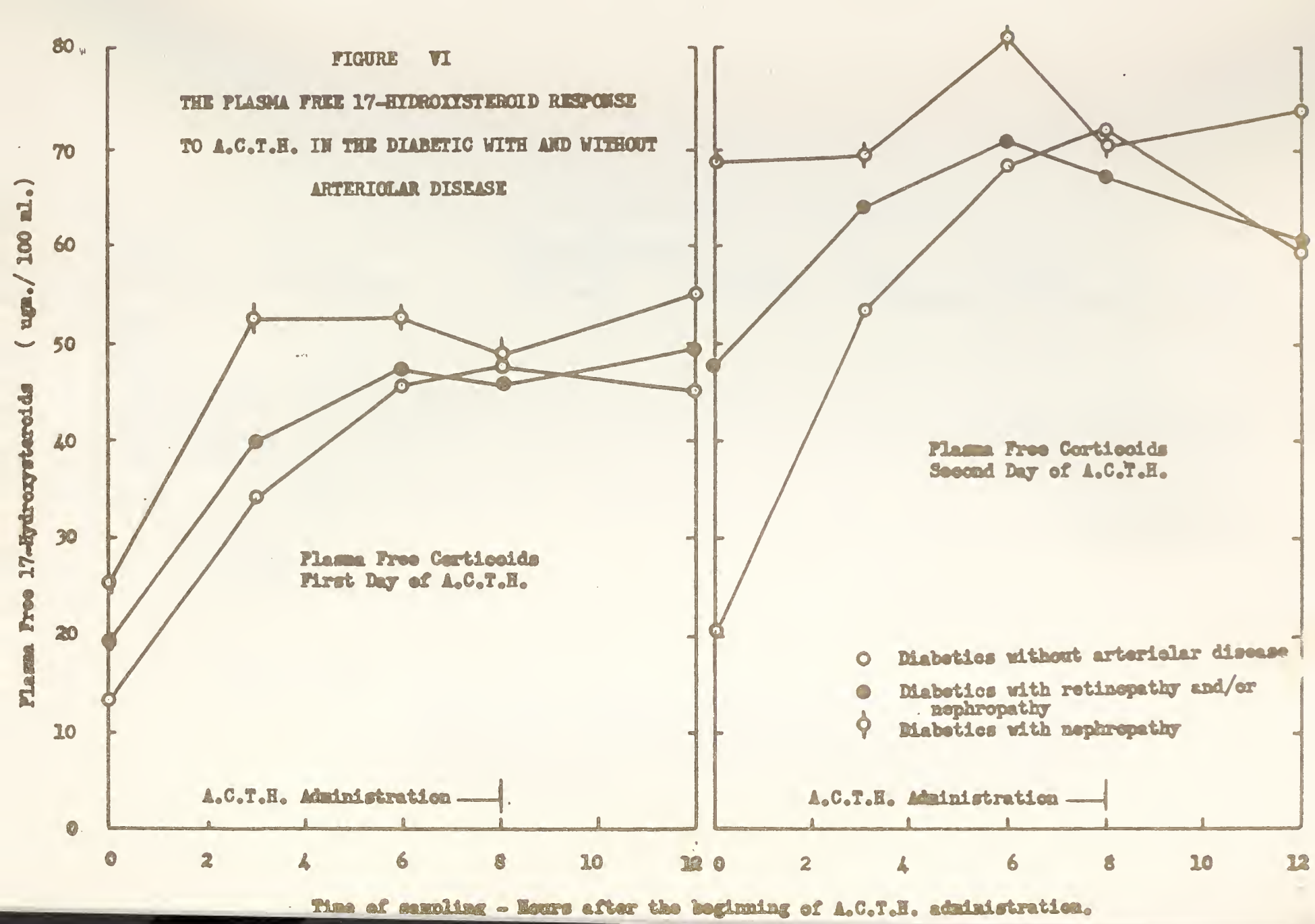
#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(15) Relationship of diabetic arteriolar disease to adrenal function. Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics with nephropathy.

FIGURE VI

THE PLASMA FREE 17-HYDROXYSTEROID RESPONSE TO A.C.T.H. IN THE DIABETIC WITH AND WITHOUT ARTERIOLAR DISEASE



Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	5	2	7	5	2	7	5	3	8	5	2	5	2	5	3
Steroid Range (mg./24 hours)	2.3 10.2	7.1 7.4	2.3 10.2	13.9 42.8	17.0 38.5	13.9 42.8	28.0 73.5	24.0 50.3	24.0 73.5	8.3 18.2	7.0 8.5	14.4 26.3	7.1 17.6	21.5 40.8	9.8 19.7
Steroid Mean (mg./24 hours)	6.1	7.3	6.5	31.4	27.8	30.4	52.2	37.8	46.8	13.3	7.7	21.4	12.4	32.5	16.0
S. D.	3.6	-	3.0	11.0	-	18.1	13.2	16.9	4.2	-	5.2	-	8.0	8.0	5.4

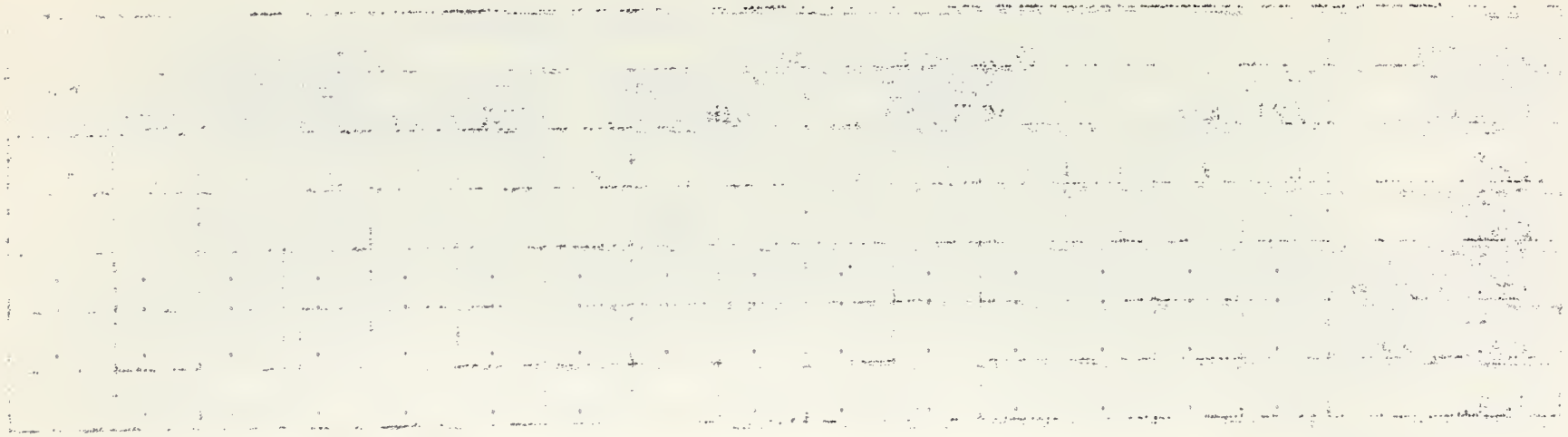
* M - Male
F - Female
T - Total (Male and Female)

TABLE II(16) Relationship of diabetic arteriolar disease to adrenal function. 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. of ACTH over an eight hour period on each of two days to diabetics without arteriolar disease.

Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	6	3	9	4	3	7	6	2	8	6	3	4	3	6	2
Steroid Range (mg./24 hours)	4.2 14.3	2.4 3.2	2.4 14.3	22.8 29.2	6.9 43.9	6.9 43.9	22.8 82.8	16.4 68.6	16.4 82.8	8.0 15.8	5.1 7.0	9.0 24.7	6.7 22.1	11.3 38.4	22.1 36.5
Steroid Mean (mg./24 hours)	8.6	2.8	6.7	26.0	19.7	23.3	36.5	42.5	38.0	12.2	6.4	18.6	12.2	26.9	29.3
S. D.	4.1	0.4	4.4	3.1	6.6	12.8	26.0	-	24.1	5.3	1.1	7.0	8.6	9.6	-

* M - Male
F - Female
T - Total (Male and Female)

TABLE II(17) Relationship of diabetic arteriolar disease to adrenal function. 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. of ACTH over an eight hour period on each of two days to diabetics with evidence of retinopathy and/or nephropathy.



Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	2	2	4	2	2	4	2	1	3	2	2	2	2	2	1
Steroid Range (mg./24 hours)	12.4 14.3	2.4 3.2	2.4 14.3	27.9 29.2	6.9 8.2	6.9 29.2	22.8 30.0	-	16.4 30.0	8.4 14.3	5.1 7.0	9.0 17.9	6.7 7.7	11.3 28.8	-
Steroid Mean (mg./24 hours)	13.4	2.8	8.1	28.6	7.5	18.1	26.4	16.4	23.1	11.3	6.4	13.5	7.2	20.0	22.1
S. D.	-	-	6.2	-	-	12.2	-	-	6.8	-	-	-	-	-	-

* M - Male
F - Female
T - Total (Male and Female)

TABLE II(18) Relationship of diabetic arteriolar disease to adrenal function. 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. of ACTH over an eight hour period on each of two days to diabetics with nephropathy.

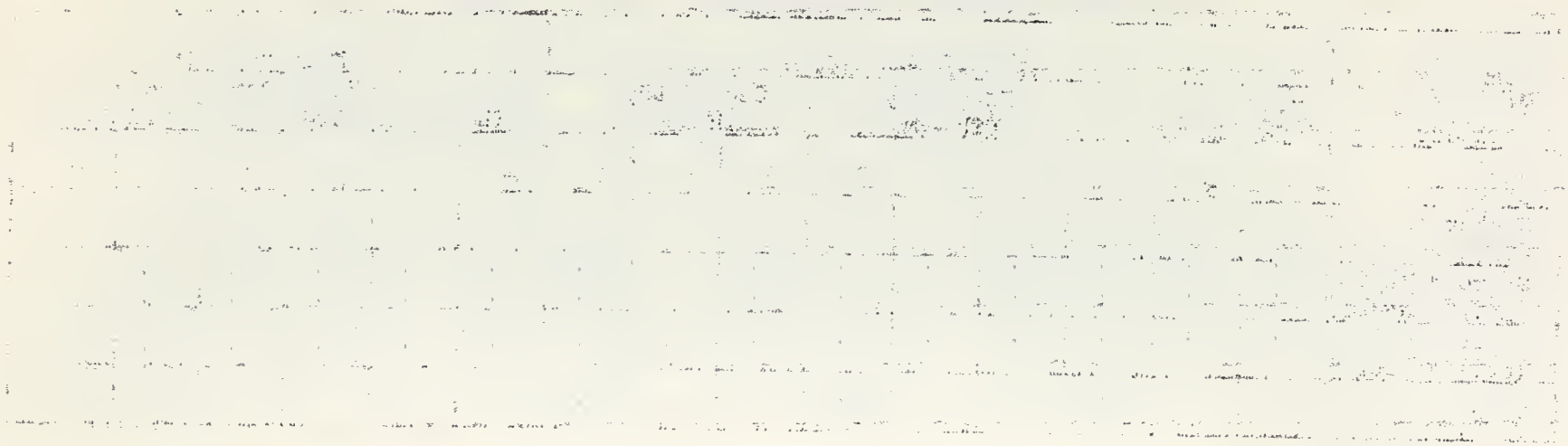
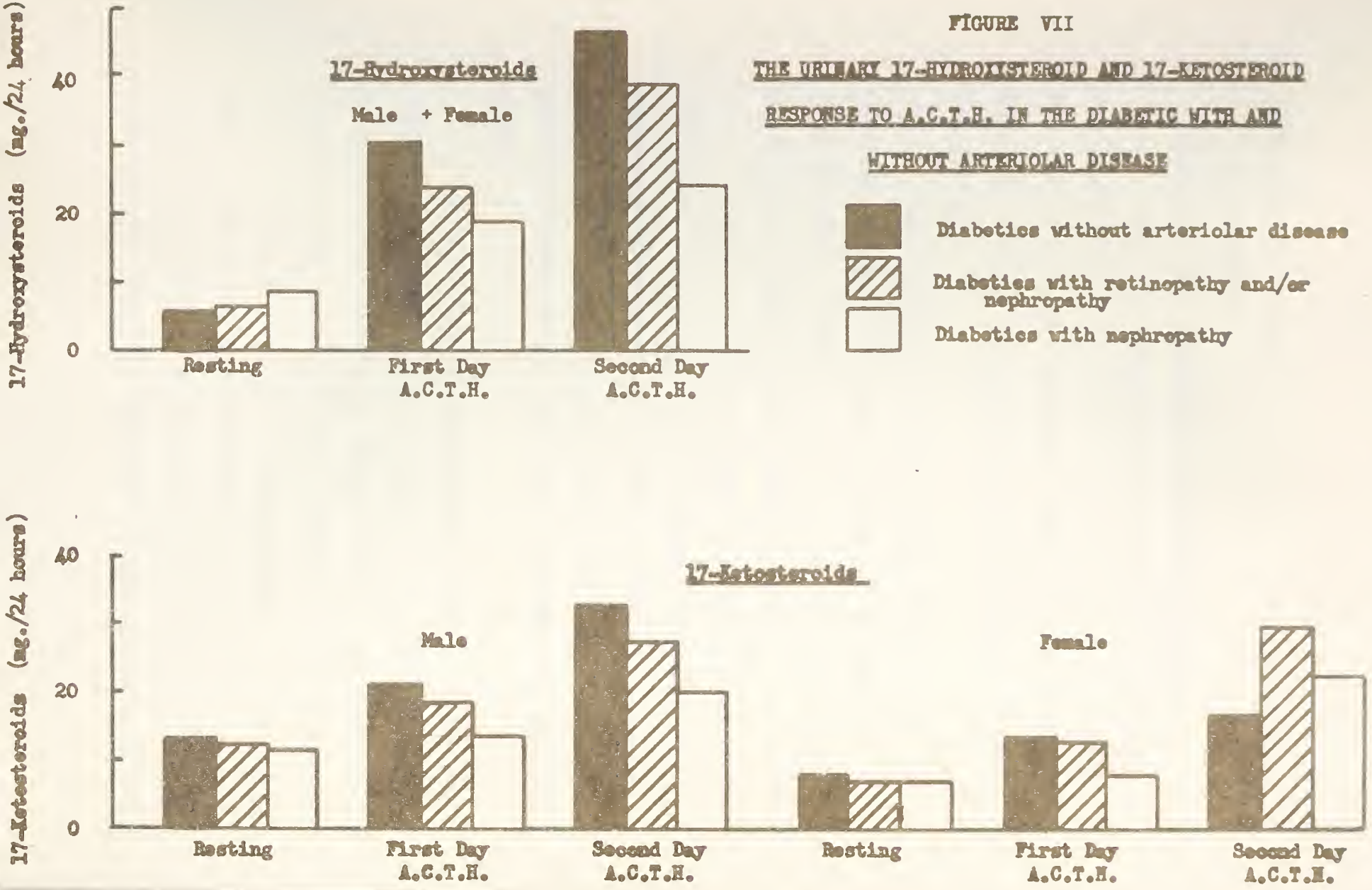


FIGURE VII

THE URINARY 17-HYDROXYSTEROID AND 17-KETOSTEROID RESPONSE TO A.C.T.H. IN THE DIABETIC WITH AND WITHOUT ARTERIOLAR DISEASE



D. Discussion of Results.

1. Urinary Studies

Comparison between diabetics and control subjects.

The urinary excretion of 17-hydroxycorticosteroids in the regulated diabetic does not appear to vary significantly from that of the control subject. (Table I (1), I (2) and Figure I). This is in agreement with the findings of others (45, 56, 59).

When compared in various age groups the diabetic in some cases excretes lower than normal amounts of urinary corticoids while in other cases the reverse hold true. Age itself does not appear to be an important factor.

There is perhaps a slightly lower excretion of urinary corticoids in females irrespective of diabetes. The only exception to this is in the diabetic female of twenty to forty years, who exhibits higher values than the equivalent male. This would probably not be found were a greater number of cases studied.

Urinary total 17-hydroxysteroids were measured. Although there is no difference between the excretion of these substances in the diabetic and control subject, many conjugated products of corticoid metabolism in addition to free metabolically active compounds are measured by this procedure. The possibility arises that there may be on factionation of these substances, some difference between the diabetic and the non diabetic person. In the presence of hepatic impairment, which may occur in diabetes,

the metabolism of corticosteroids may be altered and, although the total 17-hydroxysteroid output in the urine be normal, free corticoids could predominate.

In addition, the renal excretion of 17-hydroxysteroids may be different in the diabetic than in the control subject. Renal arteriolar disease is known to occur in diabetes in the absence of overt clinical signs of involvement. To substantiate this, a slightly reduced renal excretion of an administered dose of cortisone has been found in the diabetic (59). Perhaps overloading of the system demonstrates this defect where under conditions of normal production alone, the kidney is able to maintain a normal secretion.

As was found in 17-hydroxysteroid studies in the diabetic and non diabetic subject, urinary 17-ketosteroid excretion does not vary significantly between the two groups. In some age ranges, urinary levels are greater in the diabetic while in others the non diabetic is higher. This is probably due to the wide variation in normal values. Most reports indicate low excretion in diabetics (53, 54, 55, 56). However, Greenman et al found normal values (57).

Unlike urinary 17-hydroxysteroids, 17-ketosteroids appear to vary markedly with age in both non diabetic and diabetic patients. This is a fairly uniform inverse relationship.

Sex variation in 17-ketosteroid excretion is readily seen in Figure I, male levels being moderately higher than

female in each age group.

The age and sex variation of 17-ketosteroid excretion in diabetes has not been adequately reported in the literature. However, the findings in this control series is in agreement with what has been previously reported (82).

Comparison between diabetics with arteriolar disease and those without this complication.

In this comparison, there appears to be essentially no difference in the urinary 17-hydroxysteroid output, between these groups. (Table I (3) and Figure II).

Variation is not uniform. In the male group, retinopaths and those with nephropathy appear to excrete slightly greater amounts while in the female group, the reverse seems true. This in reality is unlikely and probably reflects the inherent variability in steroid excretion in these patients.

Urinary 17-ketosteroid excretion studies in diabetics with and without arteriolar disease again show variation between the groups. If age is taken into consideration, there is probably little difference. It would appear from Table I (3) and Figure II that diabetic males with nephropathy have increased urinary levels of 17-ketosteroids while those of the female nephropath are lower than found in the diabetic without arteriolar disease.

Most of the male nephropaths, however, are in a younger age group than are the male diabetics with arteriolar

disease. This may explain the apprent increase. Similarily, the low urinary levels found in the diabetic female with nephropathy can probably be accounted for on the basis of an uneven distribution with respect to age. The average age of female nephropaths is somewhat greater than that of the female diabetic without arteriolar disease. The possible relationship of kidney disease to adrenal steroid excretion was mentioned.

Comparison of urinary steroid excretion in diabetics with respect to insulin requirements and the duration of the disease.

There is essentially no difference in the urinary excretion of 17-hydroxysteroids and 17-ketosteroids in diabetics requiring large amounts of insulin to those requiring smaller quantities. Similarily the duration of disease does not alter the urinary output of these steroids. (Tables I (4) and I (5).

11. Urinary and Plasma Studies: Response to A.C.T.H. Comparison between diabetics and control subjects.

Plasma studies: The mean plasma free 17-hydroxycorticosteroid response to A.C.T.H. is greater in the diabetic than is found in the control patient. (Tables II (1), II (2), II (4), II (5) and Figure III). Maximal levels are attained after six to eight hours on a second day of A.C.T.H. administration. Although there is considerable overlap the maximum level found in the regulated diabetic was 133 micrograms per 100 ml. while that for non diabetes was 71.8 micrograms per 100 ml. More than half the diabetics tested had maximal levels greater than was

found in control patients. The plasma corticoid response to A.C.T.H. in diabetes has previously been reported as normal (70, 73).

Both male and female diabetics had plasma corticoid levels greater than their non diabetic counterparts. (Figure IV). In addition females in both groups were higher than males, although this difference was less marked in the non diabetic group.

The plasma mean corticoid response in three diabetics with mild acidosis was greater than that found in the regulated diabetics. (Table II (3) and II (6).

As the difference in plasma levels between diabetic and non diabetic persons is slight initially and increases with continued A.C.T.H. administration, perhaps the metabolic upset found in the diabetic under these conditions, (moderate to marked hyperglycemia, gross glycosuria and in some cases slight acetonuria), might in some way produce a greater than normal corticoid response. If this were the case it would explain the differences found between normal and diabetic persons. One experiment directed toward this end proved inconclusive. A diabetic was given intravenous A.C.T.H. in a slow infusion over an eight hour period on each of two successive days with measurement of plasma CO_2 content, blood sugar, and 17-hydroxycorticoids at various time intervals. A week later this was repeated with insulin added to the A.C.T.H. infusion.

The plasma CO_2 content remained normal on both occasions.

The blood sugar rose markedly on the first occasion, but remained within normal limits when the insulin infusion was given. Plasma corticoid response was initially lower than usually found in the diabetic. On repeat testing with insulin and A.C.T.H. these levels rose moderately.

There are several other factors which must be considered in evaluating the significance of the elevated plasma corticoid response seen in the diabetic. Plasma 17-hydroxycorticosteroid determinations involved only the estimation of the free fraction in these experiments. In the normal individual, 17-hydroxycorticosteroids are metabolized in part by the liver which forms conjugates of these with glucuronic and sulfuric acids (83). In healthy individuals there are approximately equal quantities of conjugated and free forms in the peripheral blood (81). In view of the possibility of altered liver function in diabetes, conjugation might not keep pace with the production of corticoids and hence free plasma levels might be elevated in spite of a relatively normal adrenal output. Investigation of plasma levels of both free and conjugated forms following A.C.T.H. has not been reported in diabetes mellitus.

Again, the diabetic kidney may not be able to excrete adrenal steroids at a normal rate when under the influence of A.C.T.H. for at least two reasons. Firstly, the presence of intracapillary glomerulosclerosis even though subclinical might reduce the renal excretion of steroids and secondly, an altered renal reaction to glycocorticoids may be present. Increased

renal function as evidenced by an increased glomerular filtration rate, and increased renal effective plasma loss with minimal reduction in the filtration fraction has been shown to occur in dogs when given A.C.T.H. This is due to the resultant corticoid production and not to A.C.T.H. per se (84). Perhaps the diabetic kidney is not as responsive as is the normal.

Yet another factor which should be considered and of which little is known is the rate of peripheral utilization of hydrocortisone in the diabetic.

Urinary Studies: Twenty-four hour urinary 17-hydroxysteroids and 17-ketosteroids measured prior to and during A.C.T.H. administration in diabetic and non diabetic persons were initially similar, but as with plasma corticoids, the diabetic excreted greater amounts of urinary corticoids during A.C.T.H. administration. (Table II (7) to II (9); Figure V).

The difference between the diabetic and non diabetic response is greater on a second day of A.C.T.H. administration.

The parallelism between the urinary excretion of adrenal steroids and plasma levels of these compounds tends to rule out any gross block at the kidney level, common to all diabetics. Several in this group could have such a defect without changing the overall picture.

Average urinary steroid levels in mild diabetic acidosis were lower than one would expect. This is probably not significant as only three cases were studied.

The urinary 17-hydroxysteroid values charted in Figure V are average values without regard to sex as there is little variation between males and females. The 17-ketosteroid values are plotted separately since there is a moderate sex variation.

Comparison between diabetics with arteriolar disease and those without this complication.

Plasma Studies: The plasma 17-hydroxycorticosteroid response to A.C.T.H. in diabetics with arteriolar disease is compared to that in diabetics without this complication in Tables II (10) - II (15) and Figure VI. It would appear from these that diabetics with nephropathy have higher initial plasma corticoid levels and a greater corticoid response to A.C.T.H. than do diabetics without arteriolar disease. There are, however, only four cases in the nephropathy group, two females and two males.

Sex variation may be a factor in the explanation of this finding. Females show a greater response in both the group without arteriolar disease as well as in the group with nephropathy, but the relative proportion of females to males is greater in the latter group.

Furthermore, there is a considerable overlap of values. Actually a greater plasma corticoid response was seen in some diabetics without arteriolar disease than was found in any with nephropathy irrespective of sex.

Urinary Studies: Urinary 17-hydroxysteroid and 17-ketosteroid levels prior to and during the administration of A.C.T.H. to

diabetics with and without arterial disease are recorded in Tables II (16) to II (18) and Figure VII.

Resting levels appear to be relatively equal and independant of arteriolar disease, while the response to A.C.T.H. seems to be lower in the nephropath. Here again, the number of cases studied is insufficient to be conclusive.

It is of interest to note that three of the four nephropaths had decreased urinary function as indicated by a subnormal P.S.P. excretion test. The possibility arises that the rate of urinary excretion of 17-hydroxysteroids and 17-ketosteroids may be lower in the nephropath than in the diabetic without renal arteriolar disease and thus one might expect low urinary levels in the presence of elevated plasma corticoids without there actually being any abnormality in adrenocortical function. This was discussed previously and remains speculative.

Comparison of plasma and urinary steroids in response to A.C.T.H. in diabetics with respect to insulin requirements and the duration of the disease.

There is essentially no difference in the plasma corticoids response or the urinary 17-hydroxysteroids and 17-ketosteroids response to A.C.T.H. in diabetics requiring large quantities of insulin when compared to those requiring smaller quantities. Similarily the duration of the disease does not appear to be significant. These results are tabulated in the appendix in Tables II (19) to II (30).

E. SUMMARY AND CONCLUSIONS

I. Urinary Studies

1. The twenty-four hour urinary excretion of 17-hydroxysteroids and 17-ketosteroids was measured in a group of ninety-six regulated diabetic and sixty-five non diabetic persons.

2. There appears to be no difference in the urinary excretion of 17-hydroxysteroids and 17-ketosteroids between the diabetic and the control subject.

3. Urinary 17-ketosteroid excretion varies moderately with age in both the diabetic and non diabetic person. This is an inverse relationship. There is only a suggestion of a similar variation in 17-hydroxysteroid excretion.

4. Urinary 17-ketosteroid excretion varies with sex. Levels measured in female diabetic and non diabetic are lower than those of the comparable male. A similar variation occurs in 17-hydroxysteroid excretion although this is less marked.

5. Levels of urinary 17-hydroxysteroid and 17-ketosteroid excretion in the diabetic appear to be independant of insulin requirements, the duration of the disease and the presence of arteriolar complications.

II. Plasma and urinary studies: Response to A.C.T.H.

1. Plasma free 17-hydroxysteroids with twenty-four hour urinary 17-hydroxysteroids and 17-ketosteroids were measured in response to A.C.T.H. This was given in

25 I.U. quantities in an intravenous infusion of normal saline over an eight hour period on each of two successive days. Twenty diabetic and fifteen non diabetic persons were investigated.

2. The mean plasma 17-hydroxysteroid and urinary 17-hydroxysteroid and 17-ketosteroid response to A.C.T.H. was greater in the diabetic than in the control subject. Furthermore, the difference in response was greater on the second day of A.C.T.H. administration. A possible explanation is proposed.

3. The mean female plasma corticoid response to A.C.T.H. whether in the diabetic or control group, was greater than that found in the male. Urinary studies revealed the reverse. Further studies are necessary to evaluate this finding.

4. There is a suggestion that diabetics with nephropathy show a greater plasma corticoid response to A.C.T.H. than do diabetics without this complication. Furthermore, the urinary excretion of both 17-hydroxysteroids and 17-ketosteroids in response to A.C.T.H. may be lower in the diabetic with nephropathy than in the diabetic without this complication. A possible explanation is offered, but further studies are necessary.

5. The plasma 17-hydroxycorticoid response as well as the urinary 17-hydroxysteroid and 17-ketosteroid response to A.C.T.H. appears to be independant of insulin requirements and the duration of the disease.

APPENDIX

Steroids	17-Hydroxysteroids				17-Ketosteroids			
Sex	Male		Female		Male		Female	
Duration*	L	G	L	G	L	G	L	G
Number of cases	31	30	20	16	34	31	20	19
Average age (years)	54	47	58	59	54	47	58	59
Steroid range (mg./24 hours)	1.13 12.4	2.28 19.6	1.30 8.42	0.73 12.4	4.30 23.4	5.57 33.4	2.40 22.6	4.62 14.4
Steroid mean (mg./24 hours)	5.03	7.01	4.87	4.99	13.0	14.9	7.87	8.28
S. D.	3.37	3.87	2.43	3.14	4.8	6.1	5.05	4.35

* L - Duration of diabetes nine or less years.
G - Duration of diabetes greater than nine years.

TABLE I(4) 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids. A comparison in the diabetic with respect to the duration of the disease.

Steroids	17-Hydroxysteroids				17-Ketosteroids			
Sex	Male		Female		Male		Female	
Insulin*	L	G	L	G	L	G	L	G
Number of cases	25	35	22	14	26	38	23	16
Average age (years)	62	43	60	56	62	43	60	56
Steroid range (mg./24 hours)	1.50 14.3	1.13 19.6	0.73 9.01	1.30 12.4	5.75 33.4	4.30 24.6	3.12 22.6	2.40 16.7
Steroid mean (mg./24 hours)	5.80	6.23	4.59	5.45	13.1	14.5	7.85	8.38
S. D.	3.86	3.68	2.55	3.03	6.2	5.0	4.56	3.43

* L - Those requiring thirty units or less.
G - Those requiring greater than thirty units.

TABLE I(5) 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids. A comparison in the diabetic with respect to insulin requirements.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	3	4	7	4	4	8	5	4	9	5	4	9	3	4	7
Range 17-OHCS gm./100 cc	13.0 22.3	5.4 31.4	5.4 31.4	26.8 39.7	28.6 46.0	26.8 46.0	33.0 63.6	42.8 64.9	33.0 64.9	30.1 45.9	40.8 66.6	30.1 66.6	41.7 57.8	34.9 73.3	34.9 73.3
Mean 17-OHCs ɣgm./100 cc	16.7	15.1	15.8	32.8	38.5	35.6	44.6	51.6	47.7	38.4	53.3	45.0	50.8	57.6	54.7
S. D.	4.8	6.2	8.5	6.6	7.3	7.1	14.2	10.3	12.5	6.8	12.1	11.9	8.3	16.5	13.2

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(19) Relationship of the duration of diabetes to adrenal function. Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics of nine years or less duration.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	5	2	7	6	2	8	6	2	8	6	2	8	5	2	7
Range 17-OHCS gm./100 cc	11.3 20.0	8.6 25.8	8.6 25.8	11.8 81.5	27.1 42.4	11.8 81.5	18.8 76.6	41.7 43.7	18.8 76.6	28.7 64.8	53.9 57.9	28.7 64.8	18.8 47.2	52.8 61.6	18.8 61.6
Mean 17-OHCs ¥gm./100 cc	16.8	17.2	16.9	39.4	34.8	38.2	45.4	42.7	44.8	43.9	55.9	46.9	34.2	57.0	40.7
S. D.	3.9	5.9	5.9	23.8	-	20.6	20.9	-	17.7	12.5	-	12.0	11.9	-	15.0

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(20) Relationship of the duration of diabetes to adrenal function. Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics of greater than nine years duration.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	5	4	9	5	4	9	5	4	9	5	4	9	5	4	9
Range 17-OHCS gm./100 cc	9.6 43.4	8.9 97.5	8.9 97.5	33.6 81.0	46.5 72.5	33.6 81.0	41.0 93.0	49.9 105.0	41.0 105.0	49.0 81.6	46.9 133.0	46.9 133.0	28.9 85.0	45.1 97.5	28.9 97.5
Mean 17-OHCs ¥gm./100 cc	21.1	43.4	31.0	59.5	61.3	60.3	66.9	78.8	72.2	65.3	78.5	71.7	53.1	77.0	63.7
S. D.	13.8	38.0	27.9	17.8	11.6	14.5	19.2	23.4	20.7	14.9	35.7	26.4	25.6	22.2	26.0

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(21) Relationship of the duration of diabetes to adrenal function. Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics of nine or less years duration.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	5	2	7	6	2	8	5	2	7	6	2	8	5	2	7
Range 17-OHCS gm./100 cc	8.8 57.0	41.7 77.0	8.8 77.0	28.8 62.9	73.4 79.4	28.8 79.4	42.6 72.9	75.9 86.7	42.6 86.7	52.7 81.5	72.5 88.0	52.7 88.0	31.8 74.5	22.8 88.1	22.8 88.1
Mean 17-OHCs gm./100 cc	28.9	59.4	37.6	50.4	76.4	56.9	61.5	81.3	67.1	62.3	80.3	66.8	59.4	55.5	55.0
S. D.	20.2	-	24.5	12.7	-	15.7	12.5	-	14.4	10.5	-	12.9	17.1	-	23.4

#Hours after the beginning of ACTH administration.

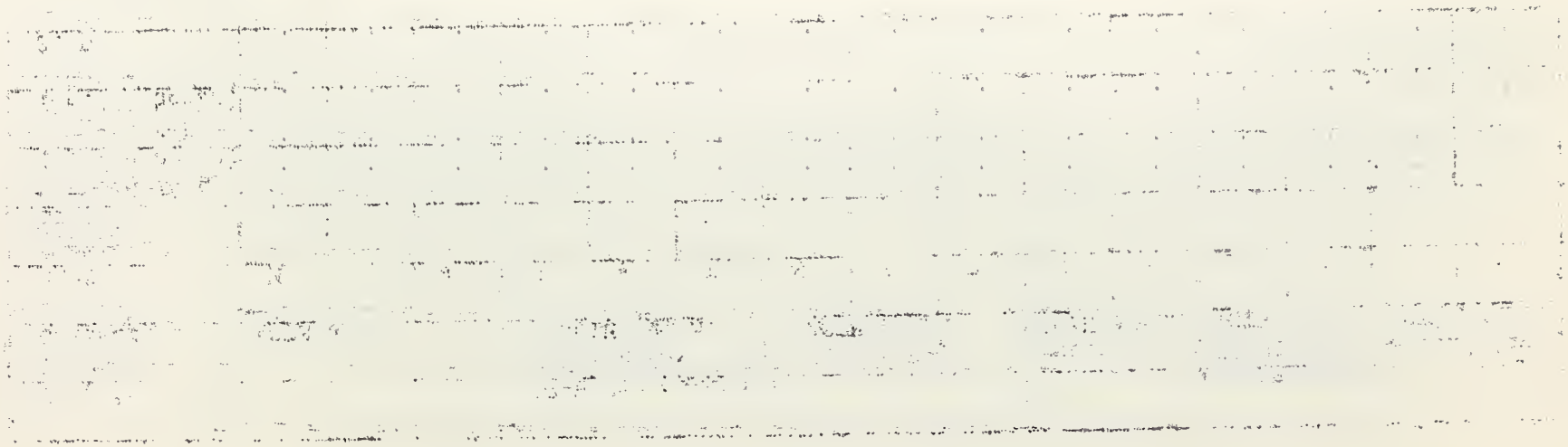
*M - Male
F - Female
T - Total (male and female)

TABLE II(22) Relationship of the duration of diabetes to adrenal function. Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics of greater than nine years duration.

Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	5	3	8	5	3	8	5	4	9	5	3	5	3	5	4
Steroid Range (mg./24 hours)	2.3 12.4	2.3 7.4	2.3 12.4	13.9 34.6	6.9 43.9	6.9 43.9	24.0 65.4	16.4 68.6	16.4 68.6	9.6 15.4	5.1 7.0	14.4 26.2	7.1 22.1	22.6 40.8	9.8 36.5
Steroid Mean (mg./24 hours)	6.7	4.2	5.8	25.8	22.6	24.6	38.7	37.0	34.2	14.0	6.4	20.9	12.3	33.0	21.8
S. D.	4.4	2.8	7.3	7.9	19.1	12.3	17.1	23.1	19.1	2.5	1.1	4.7	8.5	7.4	11.1

* M - Male
F - Female
T - Total (Male and Female)

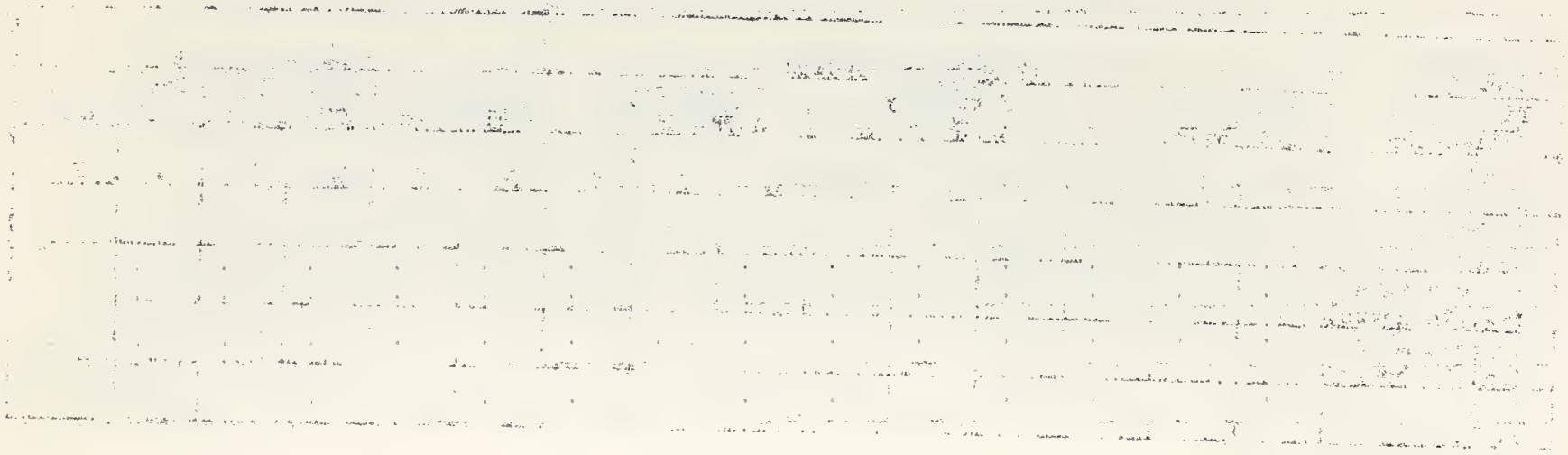
TABLE II(23) Relationship of the duration of diabetes to adrenal function. 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. ACTH over an eight hour period on each of two days to diabetics of nine or less years duration.



Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	6	2	8	4	2	6	6	1	7	6	2	4	2	6	1
Steroid Range (mg./24 hours)	4.2 14.3	3.2 7.1	3.2 14.3	23.9 42.8	8.2 38.5	8.2 42.8	22:8 82.6	-	22.8 82.6	8.0 18.2	7.0 8.5	9.0 25.7	6.7 17.6	11.3 38.4	-
Steroid Mean (mg./24 hours)	8.2	5.1	7.4	33.0	23.4	29.8	47.7	50.3	48.1	11.7	7.7	19.0	12.2	26.5	19.7
S. D.	3.8	-	3.6	8.6	-	12.7	25.2	-	23.0	4.4	-	7.8	-	9.7	-

* M - Male
F - Female
T - Total (Male and Female)

TABLE II(24) Relationship of the duration of diabetes to adrenal function. 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. ACTH over an eight hour period on each of two days to diabetics of greater than nine years duration.



Time of Sampling #	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	5	3	8	5	3	8	6	3	9	6	3	9	5	3	8
Range 17-OHCS gm./100 cc	13.0 22.3	5.4 31.4	5.4 31.4	27.6 81.5	28.6 46.0	27.6 81.5	33.0 76.6	42.8 64.9	33.0 76.6	30.1 51.1	45.7 66.6	30.1 66.6	39.9 57.8	57.0 73.3	39.9 73.3
Mean 17-OHCs ¥gm./100 cc	16.6	16.1	16.4	44.1	37.7	41.7	50.5	54.1	51.7	40.6	57.5	46.3	47.9	65.2	54.4
S. D.	3.7	13.6	7.8	21.4	8.7	17.2	17.8	11.0	15.3	8.0	10.7	11.9	7.5	8.2	11.5

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(25) Relationship of insulin requirements to adrenal function. Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics requiring thirty units or less daily.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	3	3	6	5	3	8	5	3	8	5	3	8	3	3	3
Range 17-OHCS gm./100 cc	11.3 19.9	8.6 25.8	8.6 25.8	11.8 48.4	27.1 42.4	11.8 48.4	18.8 62.4	41.7 44.1	18.8 62.4	28.7 64.8	40.8 57.9	28.7 64.8	18.8 40.0	34.9 61.1	18.8 61.1
Mean 17-OHCs ɣgm./100 cc	17.0	15.5	16.3	29.5	36.8	32.2	38.5	43.2	40.3	42.2	50.9	45.5	27.8	49.6	38.7
S. D.	5.0	9.1	6.6	13.1	8.4	11.5	16.0	1.3	12.3	13.5	9.0	12.1	11.0	13.4	16.2

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

TABLE II(26) Relationship of insulin requirements to adrenal function. Plasma 17-hydroxycorticosteroid levels on the first day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics requiring greater than thirty units of insulin daily.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	5	3	8	6	3	9	5	3	8	6	3	9	6	3	9
Range 17-OHCS gm./100 cc	9.6 57.0	29.2 97.5	9.6 97.5	33.6 69.5	58.0 72.5	33.6 72.5	41.0 75.5	72.5 105.0	41.0 105.0	49.0 81.6	63.0 133.0	49.0 133.0	28.9 85.0	41.5 97.5	28.9 97.5
Mean 17-OHCs γgm./100 cc	30.4	54.9	39.6	53.7	66.2	57.8	59.3	88.4	70.2	64.9	89.0	72.9	54.1	76.3	61.5
S. D.	19.2	37.2	27.8	11.9	7.5	11.9	12.6	16.3	19.9	13.5	38.4	25.0	22.5	27.6	25.2

#Hours after the beginning of ACTH administration.
*M - Male
F - Female
T - Total (male and female)

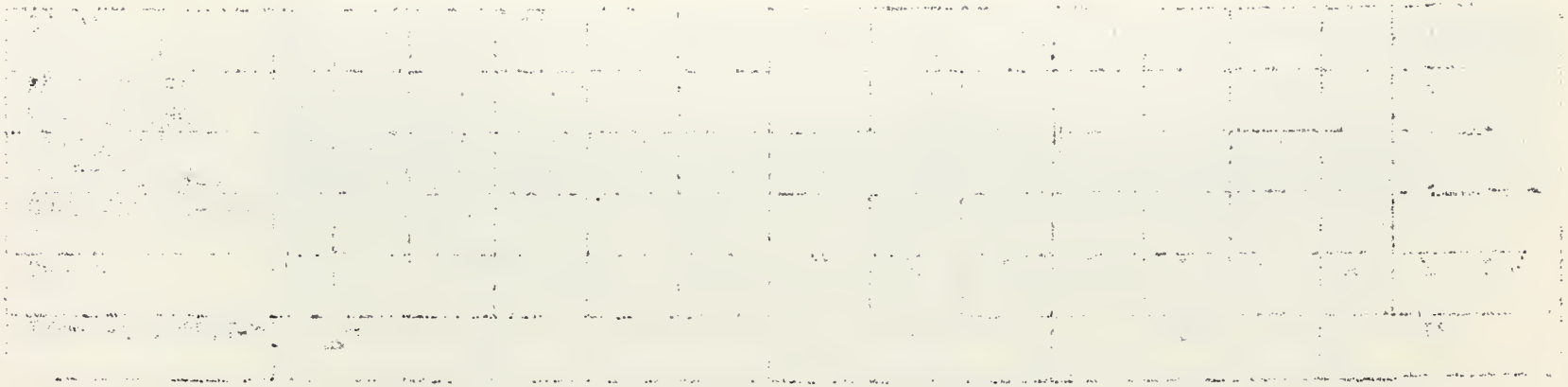
TABLE II(27) Relationship of insulin requirements to adrenal function. Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics requiring thirty units or less of insulin daily.

Time of Sampling#	0			3			6			8			12		
Sex *	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T
Number of Cases	5	3	8	5	3	8	5	3	8	5	3	8	4	3	7
Range 17-OHCS gm./100 cc	8.8 42.6	14.1 49.4	8.8 49.4	28.8 81.0	46.5 79.4	28.8 81.0	42.6 93.0	49.9 86.7	42.6 93.0	52.7 81.5	46.9 88.0	46.9 88.0	31.8 74.5	22.8 88.1	22.8 88.1
Mean 17-OHCs gm./100 cc	19.6	42.5	27.6	55.5	66.4	59.6	69.1	70.8	69.7	62.3	69.1	64.8	53.8	63.3	57.9
S. D.	13.7	34.1	24.2	19.2	17.5	18.2	17.9	18.9	17.0	11.7	20.6	14.6	20.6	37.2	25.6

#Hours after the beginning of ACTH administration.

*M - Male
F - Female
T - Total (male and female)

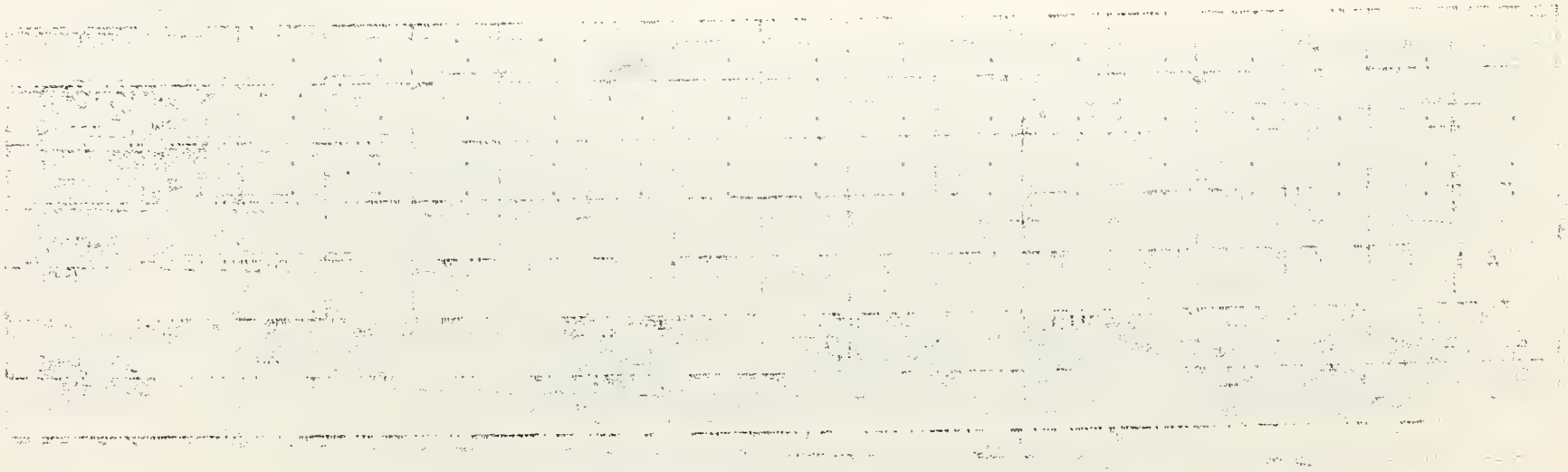
TABLE II(28) Relationship of insulin requirements to adrenal function. Plasma 17-hydroxycorticosteroid levels on the second day of the intravenous administration of 25 i.u. of ACTH over an eight hour period to diabetics requiring greater than thirty units of insulin daily.



Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	6	3	9	5	2	7	6	3	9	6	3	5	2	6	3
Steroid Range (mg./24 hours)	2.3 14.3	2.4 7.4	2.3 14.3	13.9 34.6	6.9 43.9	6.9 43.9	22.8 65.4	16.4 68.6	16.4 68.6	8.4 15.4	5.1 7.0	9.0 26.2	7.7 22.1	11.3 40.8	18.6 36.5
Steroid Mean (mg./24 hours)	7.2	4.2	6.2	26.8	25.4	26.4	37.6	41.4	38.9	12.3	6.4	18.1	14.9	32.0	25.7
S. D.	5.2	2.7	4.6	7.7	-	12.4	15.7	26.2	18.2	3.0	1.1	6.9	-	11.0	9.5

* M - Male
F - Female
T - Total (Male and Female)

TABLE II(29) Relationship of insulin requirements to adrenal function. 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. ACTH over an eight hour period on each of two days to diabetics requiring thirty or less units of insulin daily.



Steroids	17-Hydroxysteroids									17-Ketosteroids					
Time of Collection	Prior to ACTH Admin.			First Day ACTH Admin.			Second Day ACTH Admin.			Prior to ACTH Admin.		First Day ACTH Admin.		Second Day ACTH Admin.	
Sex*	M	F	T	M	F	T	M	F	T	M	F	M	F	M	F
Number of Cases	5	2	7	4	3	7	5	2	7	5	2	4	3	5	2
Steroid Range (mg./24 hours)	4.8 10.2	3.2 4.1	3.2 10.2	22.8 42.8	8.2 38.5	8.2 42.8	24.0 82.8	24.0 50.3	24.0 82.8	8.0 18.2	7.0 8.5	17.7 25.7	6.7 17.6	21.5 34.9	9.8 19.7
Steroid Mean (mg./24 hours)	7.9	5.1	7.1	31.7	21.2	27.2	50.9	37.2	47.0	13.1	7.7	22.7	10.5	26.4	14.7
S. D.	2.1	-	2.5	9.9	15.6	12.7	26.4	-	23.8	4.7	-	3.5	6.2	5.3	-

* M - Male
F - Female
T - Total (Male and Female)

TABLE II(30) Relationship of insulin requirements to adrenal function. 24-Hour urinary 17-hydroxysteroids and 17-ketosteroids prior to and during the intravenous administration of 25 i.u. ACTH over an eight hour period on each of two days to diabetics requiring greater than thirty units of insulin daily.

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